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CONFIDENTIAL DISCLOSURE AGREEMENT

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, National Institute of Allergy and Infectious Diseases ("NIAID"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS") and Pfizer Inc. ("Pfizer") (each a "Party" and collectively, the "Parties"), intending to be legally bound as of the date of the last signature hereto ("Effective Date"), agree that:

1. A Party ("Disclosing Party") may disclose information to the other ("Receiving Party") for the purpose of (b)(4) (b)(4) ("Purpose"). The Disclosing Parties are: NIAID and Pfizer.

2. The information disclosed under this Agreement ("Confidential Information") is described as:

   For Pfizer: (b)(4) (b)(4)

   For NIAID: (b)(4)

3. The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its and its affiliates' employees, investigators from the AIDS Clinical Trials Group (ACTG), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Cardiothoracic Surgical Trials Network (CTSN), Prevention and Early Treatment of Acute Lung Injury (PETAL), employees of National Heart, Lung, and Blood Institute (NHLBI) involved in the oversight and management of CTSN and PETAL, employees of the Foundation for the National Institutes of Health (FNIH) involved the ACTIV program, and the U.S. Department of Veterans Affairs (VA), consultants or contractors to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information.

4. The Receiving Party's duties under this Agreement shall apply to any Confidential Information shared orally or in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked "Confidential." Oral disclosures must be reduced to writing, marked

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(b)(4)

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure in the possession of the Receiving Party; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party, without reference to the information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return all Confidential Information received, except that the Receiving Party (i) may retain in its confidential files one (1) copy of written Confidential Information for record purposes only (b)(4)
(b)(4)

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required (b)(4)
(b)(4) to disclose any of the Confidential Information, (b)(4)
(b)(4)

8. (b)(4)
(b)(4)

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(b)(4)

9. Each Party will comply with any and all applicable import, export, and economic sanctions laws and regulations relating to its performance under this Agreement. Each Party will not, for activities under this Agreement, (1) engage in any such activities in a Restricted Market; (2) involve individuals ordinarily resident in a Restricted Market; or (3) involve companies, organizations, or governmental entities from a Restricted Market. Each Party agrees that it will not knowingly transfer to the other any goods, software, technology, information, or services that are (a) controlled at a level other than EAR99 under the U.S. Export Administration Regulations; (b) controlled under the U.S. International Traffic in Arms Regulations (ITAR); (c) specifically identified as an E.U. Dual Use Item; or (d) on an applicable export control list of a foreign country. Each Party certifies that (i) it is not on any Restricted Party list; and (ii) it is not owned or controlled by any individual or entity on any Restricted Party list. As used herein, "Restricted Market(s)" means the Crimean Peninsula, Cuba, the Donbass Region, Iran, North Korea, Sudan, and Syria, or any other country or region subject to sanctions by the United States or European Union; and "Restricted Party(ies)" means an individual or entity on the list of sanctioned entities maintained by the United Nations; the Specially Designated Nationals List and the Sectoral Sanctions Identifications List of the U.S. Treasury Department's Office of Foreign Assets Control; the U.S. Denied Persons List, the U.S. Entity List, and the U.S. Unverified List of the U.S. Department of Commerce; entities subject to restrictive measures and the Consolidated List of Persons, Groups and Entities Subject to E.U. Financial Sanctions, as implemented by the E.U. Common Foreign and Security Policy; the List of Excluded Individuals / Entities published by the U.S. Health and Human Services Office of Inspector General; any lists of prohibited or debarred parties established under the U.S. Federal Food Drug and Cosmetic Act; the list of parties suspended or debarred from contracting with the U.S. government; and similar lists of restricted parties maintained by the governmental authorities of the countries that have jurisdiction over the activities conducted under this Agreement.

10. (b)(4)

11. (b)(4)

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(b)(4)

12. (b)(4)

13. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for (b)(4) years from the Effective Date.

14. Notices or other communications required to be sent to NIAID under this Agreement shall be sent in writing and addressed to Wade Green, Technology Transfer & Intellectual Property Office, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Ste 6D Rockville, MD 20852, email: (b)(6) @niaid.nih.gov. Notices required to be sent to Pfizer under this Agreement shall be in writing and addressed to Pfizer Inc., (b)(6) New York, NY (b)(6) Attn: Business Development Contract Notice; with a copy (which will not constitute notice) to Pfizer Inc., (b)(6) (b)(6) New York, NY (b)(6) Attn: Chief Counsel; and an email to (b)(6) @pfizer.com.

15. This Agreement may be executed in any number of counterparts. (b)(4)

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Institute of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH)
5601 Fishers Lane, Ste 6D
Rockville, MD 20852

Authorized Signature:

DocuSigned by:
Wade Green
A2FB83D9211C4A8...

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date: (b)(4), 2021

Pfizer Inc.
(b)(6)
New York, NY (b)(6)

Authorized Signature:

DocuSigned by:
(b)(6)
2891176B0891493...

(b)(6)
(b)(6)
(b)(6)
(b)(6)

Date: (b)(4), 2021

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IND/RA SPONSOR: NIAID (DCR)

CLINICAL TRIAL AGREEMENT

BETWEEN

DIVISION OF CLINICAL RESEARCH (DCR), NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

&

PFIZER INC.

Based on

Protocol ACTIV3/INSIGHT014

A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of
the Safety and Efficacy of Investigational Therapeutics for
Hospitalized Patients with COVID-19
Short Title: Therapeutics for Inpatients with COVID-19 (TICO)

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The **National Institute of Allergy and Infectious Diseases ("NIAID")**, an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the **Division of Clinical Research ("DCR")**, and **Pfizer Inc.** (the "Company"), located at (b)(6) New York, NY (b)(6) (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial designated as Protocol **ACTIV3/INSIGHT014**, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)."

This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). NIAID (DCR) will conduct this Clinical Trial with a consortium of clinical trial networks under the leadership and coordination of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). Other participating networks include the AIDS Clinical Trials Group (ACTG) under the terms of their Award with NIAID, as well as the Prevention and Early Treatment of Acute Lung Injury (PETAL) and the Cardiothoracic Surgery Trial Network (CTSN) under the terms of their Awards from National Heart Lung Blood Institute (NHLBI), and the U.S. Department of Veterans Affairs (VA). In the event that any other Clinical Research Sites funded by NIAID are included in this Clinical Trial in order to complete enrollment, these sites will meet NIAID standards for clinical research sites conducting research sponsored by NIAID. The Clinical Research Sites and their respective Investigators are not parties to this Agreement.

This Agreement sets forth the terms and conditions under which this Clinical Trial will be conducted and managed.

Company and NIAID (DCR) agree as follows:

1. DEFINITIONS

The terms listed in this Section will carry the meanings indicated throughout this Agreement. To the extent that a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code ("U.S.C.") or the Code of Federal Regulations ("C.F.R."), the definition in the U.S.C. or C.F.R. will control.

"**ACTG**" means the AIDS Clinical Trials Group network sponsored and funded by NIAID in accordance with the terms of an Award.

"**Adverse Event**" or "**AE**" means the definition as stated in the Protocol.

"**Affiliate**" means, with respect to Company, (i) any legal entity of which the securities or other ownership interests representing fifty percent (50%) or more of the equity or fifty percent (50%) or more of the ordinary voting power or fifty percent (50%) or more of the general partnership interest are, at the time such determination is being made, owned,

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controlled, or held, directly or indirectly, by such legal entity; or (ii) any legal entity which, at the time such determination is being made, is controlling or under common control with, such legal entity. As used herein, the term "control," whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract, or otherwise.

"**Agreement**" means this Clinical Trial Agreement ("**CTA**"), all executed amendments and supplements to this Agreement, and all schedules, appendices and/or addenda to this Agreement.

"Award" means any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between a Government agency and the awardee, who may subcontract with the Clinical Research Sites.

"**CTSN**" means the Cardiothoracic Surgery Trials Network (CTSN) funded by NHLBI in accordance with the terms of an Award.

"**Case Report Form**" or "**CRF**" means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Clinical Research Sites**" means the clinical research sites designated as INSIGHT sites and any other sites described in the introductory paragraph where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Trial**" means a biomedical or behavioral research study of Human Subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, or devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. In this Agreement, Clinical Trial means the clinical trial for the Protocol.

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"**Confidential Information**" means confidential scientific, proprietary, business and/or financial information, provided that Confidential Information does not include:

(a) Information that is publicly known or subsequently becomes publicly known through no fault of the receiving Party;

(b) Information that is presently known or becomes known to the receiving Party from its own independent sources, without restriction as to confidentiality or use, from a person having the legal right to disclose the data;

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(c) Information that can be established by competent proof was already known and lawfully in the possession of the receiving Party at the time of the disclosure, without restriction as to confidentiality or use;
(d) Information that is independently created or compiled by the receiving Party without reference to or use of the Confidential Information and such independent development can be documented by receiving Party with written records.

"**Critical Event**" means any unanticipated study-related incident that is likely to cause or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity.

"**Data and Safety Monitoring Board**" or "**DSMB**" means an independent group of experts that advises NIAID (DCR) and the Investigators. The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (2) make recommendations to NIAID (DCR) concerning the continuation, modification, or termination of the Clinical Trial.

"**Effective Date**" means the date of the last signature of the Parties executing this Agreement.

"**Electronic Common Technical Document**" or "**eCTD**" means the standard format for electronic regulatory submissions as per 21 U.S.C. § 379k-1, "Electronic Format for Submissions," and as further described in FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," 80 Federal Register 26057 (2015).

"**FDA**" means the U.S. Food and Drug Administration.

"**Government**" means the Federal Government of the United States of America.

"**Health Authority**" or "**HA**" means any non-U.S. Health Authority used when the Clinical Trial is being conducted in whole or in part at a non-U.S. Clinical Research Site requiring the use of non-U.S. regulatory agencies.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. § 46.102(e)(1), a living individual about whom an Investigator conducting research:
(a) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimen; or
(b) Obtains, uses, studies, analyzes or generates Identifiable Private Information or identifiable biospecimens.

"**ICH**" means the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Cited are:
ICH E3: "Structure and Content of Clinical Study Reports."

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ICH E6: "Good Clinical Practice: Consolidated Guidance," published in the Federal Register [83 Federal Register 8882 (2018)]. Also referred to as "FDA/HA Good Clinical Practice Guidelines."

"**Identifiable Private Information**" or "**IPI**" about a Human Subject means private information from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**IND**" means an "**Investigational New Drug Application**," filed in accordance with 21 C.F.R. Part 312, under which clinical investigation of an experimental drug or biologic (Study Product) is performed in Human Subjects in the U.S., or intended to support a U.S. licensing action.

"**INSIGHT**" means the International Network for Strategic Initiatives in Global HIV Trials funded under combination of (1) a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI) and (2) an Award from NIAID to the University of Minnesota.

"**Institutional Review Board**" ("**IRB**") or "**Independent Ethics Committee**" ("**IEC**") means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects, and 21 C.F.R. Part 56, Subpart C: IRB Functions and Operations, as amended April 1, 2013, and other applicable regulations, an independent body comprising medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of the Human Subjects involved in a clinical trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**Invention**" means any invention or discovery that is or may be patentable or otherwise protectable under Title 35 of the U.S.C.

"**Investigator**" means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Study Product to a Human Subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, Investigator means the individual(s) identified as responsible for the conduct of the Clinical Trial at any of the participating Clinical Research Sites.

"**Investigator's Brochure**" or "**IB**" means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Study Product, including animal screening, preclinical toxicology and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the Study Product or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Study Product.

"Leidos Biomedical Research" means the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory activities related to NIAID (DCR)'s

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clinical research. Leidos operates pursuant to a NIAID statement of work covering the Protocol, contained within an Award between Leidos and the National Cancer Institute (NCI).

"**Office for Human Research Protections**" or "**OHRP**" means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"**Patent**" means any issued U.S. patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

"PETAL" means Prevention and Early Treatment of Acute Lung Injury, a clinical trials network funded by NHLBI in accordance with the terms of an Award.

"**Protected Health Information**" or "**PHI**," as defined in 45 C.F.R. Parts 160 and 164, under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), includes any *individually identifiable* health information. *Identifiable* refers not only to data that is explicitly linked to a particular individual; it also includes health information with data items which reasonably could be expected to allow individual identification.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV3/INSIGHT014, "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)" and any company/product specific associated appendices. The Protocol describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. The Agreement will be governed by the most recent version of the Protocol, and should the Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement, the terms of the Agreement will govern.

"**Protocol Team**" means the team responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. The Protocol Team will include the protocol chair (an Investigator), representatives from Company, other Investigators, representatives from NIAID (DCR), and the persons involved with statistical and data analysis for the Clinical Trial. Participation on the Protocol Team will be as agreed by the Parties and will take into account any special requirements of the Protocol design.

"**Regulatory Application**" or "**RA**" means an IND-equivalent, non-U.S. Regulatory Application, applicable when the Clinical Trial is being conducted in whole or in part at a non-U.S. clinical research site.

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"**Sponsor**" means, in accordance with the definition in 21 C.F.R. § 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with Study Product. The Office of Clinical Research Policy and Regulatory Operations within the NIAID Division of Clinical Research is the IND/RA holder and sponsor of record for this agreement. Additionally, in accordance with 21 C.F.R. § 312.52(a) and any applicable HA requirements, several sponsor responsibilities will be transferred to the University of Minnesota Statistical and Data Management Center and to Leidos Biomedical Research.

"**Statistical and Data Management Center**" or "**SDMC**" means the management center at the University of Minnesota responsible for providing statistical and data management services for INSIGHT clinical trials, including the Clinical Trial that is the subject of this Agreement in accordance with the terms of a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI). The SDMC subcontracts with International Coordinating Centers (ICCs) that work with clinical sites in many different countries and with a drug distribution company that has drug depots in the United States and the United Kingdom. References to the SDMC in this document refer to the University of Minnesota and the ICCs and drug distribution company with which they subcontract.

"**Study Product**" means, in accordance with 21 C.F.R. § 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301, *et seq*., Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended. In this Agreement, (b)(4) referred to as the Study Product.

"VA" means the U.S. Department of Veterans Affairs.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 Company acknowledges that NIAID and NHLBI fund the Clinical Research Sites under Awards, and therefore, the Clinical Research Sites have certain existing contractual or other legal obligations to NIAID and NHLBI.

2.2 Company will not provide any funding or material for any aspect of the Clinical Trial to any Clinical Research Site participating in the Clinical Trial without prior written notification to NIAID (DCR). In addition, subject to Section 14.4 of this Agreement, Company will not enter into any separate agreements, including, but not limited to, material transfer agreements, with the Clinical Research Sites or the Investigators at the Clinical Research Sites that interfere with the conduct of this Clinical Trial.

2.3 NIAID (DCR) hereby certifies any person, including Investigators, and organization engaged to perform the Clinical Trial are appropriately qualified and experience, and that

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it, SDMC, Leidos Biomedical Research, nor any of their subcontractors, did not and will not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:
(i) debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or
(ii) suspended by OHRP as a clinical research site under 45 C.F.R. Part 46.

2.3.2 Any person convicted of a felony under federal law for conduct:
(i) relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application (NDA), Biologics License Application (BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or
(ii) otherwise relating to the regulation of any drug product or medical device under the FDCA.

2.3.3 Any person performing services in connection with this Clinical Trial who has been disqualified as a clinical investigator under 21 C.F.R. § 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required by 21 C.F.R. § 312.53.

2.4 If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party immediately.

2.5 The Awards require and NIAID will ensure that the Investigators at Clinical Research Sites conduct the Clinical Trial in accordance with applicable provisions of ICH E6: FDA/HA Good Clinical Practice Guidelines, and requires that they comply with all applicable U.S., foreign government, state and local laws, regulations and guidelines.

2.6 Company agrees that this Protocol will be conducted only at sites as defined by NIAID (DCR), SDMC, and collaborating networks. However, Company can conduct, at its own expense and under its own IND, additional clinical trials with the Study Product, at non-NIAID funded sites. Company agrees to inform NIAID (DCR) in writing of any other clinical trials it may support for the use of the Study Product that would compete with this Clinical Trial for the same Human Subject population.

2.7 If Protocol-specified assays expected to be included in a regulatory submission are performed in laboratories not monitored by NIAID (DCR), Company warrants that such laboratories will comply with Good Clinical Laboratory Practice (GCLP) and all applicable regulatory requirements. Company will provide NIAID (DCR) with results of such assays and, upon request, provide documentation to support that the testing and laboratory operations are compliant with GCLP and all applicable regulatory

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requirements. NIAID (DCR), through its contractor, may audit the laboratory(ies) to ensure compliance with GCLP and all applicable regulatory requirements.

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND/RA.** NIAID (DCR) will be responsible for the submission of, and will maintain at all times during the Clinical Trial an IND/RA covering the Protocol to the FDA/HA. The IND/RA will satisfy all of the requirements of the FDA/HA, and, as applicable, will comply with eCTD format requirements. Company agrees to provide all requested documents to NIAID (DCR) in eCTD format. Company will provide a letter granting the FDA/HA permission to cross-reference Company's pertinent Master File (MF), New Drug Application (NDA), Biologics License Application (BLA), and/or IND/RAs in support of the NIAID (DCR)'s IND/RA, and in return, NIAID (DCR) will also provide a letter to Company, if requested, granting the FDA/HA permission to cross-reference the IND/RA filed by NIAID (DCR) for this Clinical Trial. NIAID (DCR) will provide a copy of all IND/RA submissions to Company at the time they are submitted to the FDA/HA. Any Confidential Information of another party will be removed.

3.2 NIAID (DCR) may delegate regulatory obligations to one or more third parties to apply for and maintain the RA and to facilitate NIAID's oversight, monitoring, and administration of the Clinical Trial at Clinical Research Sites outside of the United States. NIAID (DCR)'s third party delegate(s) will submit any clinical trial application and subsequent reports to all applicable HAs outside of the United States.

3.3 **Clinical Research Site Monitoring and Audits.** NIAID (DCR) or their designeee, will be responsible for Clinical Research Site monitoring in accordance with the clinical monitoring plan. Monitoring will be done in compliance with applicable provisions of the FDA/HA Good Clinical Practice Guidelines (ICH) (E6). NIAID (DCR) will communicate any Critical Events to Company in a timely manner, but in no event longer than seven (7) business days from when NIAID becomes aware of the Critical Event (b)(4)
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3.4 **Adverse Event Reporting.**

3.4.1 NIAID (DCR) will collect Adverse Event reports according to the procedure outlined in the Protocol and in timeframes consistent with 21 C.F.R. § 312.32. The Clinical Research Sites will report Adverse Events to NIAID (DCR) in a timely manner and in accordance with the Protocol and Protocol Instruction Manual. NIAID (DCR) will assume responsibility for the reporting of Adverse

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Events to the FDA/HA and will provide copies of all of the safety reports to Company. Such reports will be sent to:

(b)(6)
E-mail: (b)(6)
(b)(6)

(b)(6)
E-mail: (b)(6)

3.4.2 NIAID (DCR) will report all SUSARs/IND Safety Reports for participants exposed to the Study Product and matched placebo observed in this Clinical Trial to the FDA/HA and Company on a timely basis consistent with 21 C.F.R. § 312.32 and the Protocol. NIAID (DCR) will report other serious and non-serious adverse events to the FDA/HAand to Company on a timely basis consistent with 21 C.F.R. § 312.33 and the Protocol.

3.4.3 NIAID (DCR) will report all Serious Adverse Events ("SAEs") for participants exposed to the Study Product and matched placebo observed in this Clinical Trial to the FDA/HA consistent with the applicable regulations and to Company at the Safety Reports Address listed in the Contacts section within fifteen (15) calendar days of awareness. Company agrees not to contact the Clinical Research Sites directly for information related to Adverse Events. Company shall contact the NIAID (DCR) Safety Office for information related to SAEs.

3.4.4 As the manufacturer, Company will, in a timely manner consistent with FDA/HA requirements and during the term of this Clinical Trial, provide NIAID (DCR) with any information it now has or may obtain in the future regarding the safety and/or the toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial. NIAID (DCR) will promptly transmit that information to all Investigators. Such information shall be sent to:

NIAID Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
Email: rchspsafety@mail.nih.gov

3.4.5 During the course of the study, if Company is requested by a regulatory agency to unblind an SAE or SUSAR report, the NIAID (DCR) will collaborate with Company to determine whether the report can be unblinded without undermining the scientific integrity of the Clinical Trial. NIAID (DCR) will provide the blinding codes for study subjects randomized to the Study Product or the placebo to the Study Product to Company when all data forms have been keyed into the

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database for all subjects, data cleaning has been completed, and the Protocol Team has declared the study data set to be complete

3.5 **Pregnancy Reporting.** NIAID (DCR) will report pregnancies with respect to Study Product to Company no later than thirty (30) days of becoming aware of such events.

4. SAFETY MONITORING

Data and Safety Monitoring Board (DSMB). A NIAID DSMB will monitor this Clinical Trial as described in the Protocol. NIAID will notify Company in advance of any DSMB review. NIAID will provide recommendations derived from the DSMB to Company.

5. FDA/HA MEETINGS/COMMUNICATIONS

5.1 With respect to any discussions with the FDA/HA involving data obtained from this Clinical Trial under NIAID (DCR)'s IND/RA, NIAID (DCR), in consultation with Company, will take the initiative in arranging meetings or conference calls with the FDA/HA. Formal meetings with the FDA/HA concerning the Clinical Trial design and/or data will be discussed and agreed upon in advance by Company and NIAID (DCR). Company will have the right to participate in all formal meetings with the FDA/HA. Company agrees not to contact the FDA/HA independently of NIAID (DCR) concerning this Clinical Trial. However, Company may contact the FDA/HA on separate product-related issues. NIAID (DCR) will provide Company with copies of all transmittal letters for IND/RA submissions, and formal questions and responses that have been submitted to the FDA/HA. Any Confidential Information of another party will be removed.

5.2 Company will promptly notify NIAID (DCR) of:

(a) Any FDA/HA correspondence related to the Protocol that is received by Company, or its Affiliates; and
(b) FDA/HA enforcement actions directed toward Company or its Affiliates, including, but not limited to, warning letters, seizures, or recalls; injunctions/consent decrees; rejection of regulatory submissions or withdrawal of approval for the Study Product; and
(c) Criminal investigations involving the Clinical Trial or the Study Product; and
(d) Proceedings to debar Company or its Affiliates or individuals employed under a contract to Company and/or its Affiliates, who are directly involved in the Clinical Trial or the Study Product.

5.3 Each Party will also promptly notify the other Parties of any action taken by the FDA/HA regarding the Study Product that would impact the safety of Human Subjects in the Clinical Trial.

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6. SUPPLY, DISTRIBUTION AND USE OF STUDY PRODUCT

6.1 **Supply.** NIAID (DCR) and the SDMC shall provide Company with an estimate of the quantity of Study Product that will be required to complete the Protocol. Company will supply the Study Product to NIAID (DCR) without charge and in quantities and conditions sufficient to complete the Protocol and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Study Product. Company will be responsible for labeling the Study Product used in the Clinical Trial.

6.2 **Distribution.**

6.2.1 Company will ship the Study Product to central distribution drug depot(s) to be arranged by NIAID and the SDMC as mutually agreed by the Parties. Company will provide specific storage and/or shipping instructions for the Study Product to NIAID (DCR), the SDMC, the central distribution drug depot(s), and/or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. Company warrants that any packaging for hazardous material, provided by Company, meets U.S. Department of Transportation regulatory requirements for use at all U.S. Clinical Research Sites.

6.2.2 (b)(4)

6.2.3 If there is evidence that the Study Product that arrived at the central distribution drug depot(s) has not been maintained according to the defined shipping instructions, or is potentially adulterated, the SDMC will contact Company to inform it of the condition of the received Study Product and to determine if the Study Product is usable or if it must be replaced. If the Study Product must be replaced, Company will replace it at no cost to NIAID (DCR), the central distribution drug depot(s), or the Clinical Research Sites.

6.3 **Use.** NIAID (DCR) and the SDMC will not transfer the Study Product to parties other than the central distribution drug depot(s) or the Clinical Research Sites, nor will NIAID (DCR) or the SDMC chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed in writing by the Parties. NIAID (DCR), pursuant to the Awards, will ensure that the Investigators: (i) use the Study Product only in accordance with the Protocol and for no other purpose; (ii) do not transfer the Study Product to any parties except Company, the central distribution drug depot(s), or the Clinical Research Sites; and (iii) do not chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed to, in writing, by the Parties.

6.4 **Study Product Return.** Upon completion of the Protocol, NIAID (DCR) and the SDMC, will ensure destruction or, at Company's request, return any unused Study

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Product to Company.

6.5 **Study Product.** Company represents that when shipped by Company, the Study Product supplied (b)(4)

6.6 **Source.**

6.6.1 In the event Company elects to terminate its development of Study Product for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to NIAID (DCR) within ninety (90) days of discontinuation then in accordance with the terms of this Agreement, including but not limited to Section 8, Company will provide NIAID (DCR) with Study Product sufficient to complete the Clinical Trial as set forth in the Protocol.

6.6.2 The Parties also agree that should this Agreement be terminated prior to completion of the Protocol, the Protocol will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol and Company will supply enough Study Product to complete the Protocol.

7. INVESTIGATOR'S BROCHURE (IB)

Company will provide a current IB in eCTD format for all applicable components of the Study Product, and any later revisions and addenda to the IB for the Study Product, including a summary of changes (SOC), to NIAID (DCR), as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Section 13 (Confidential Information) of this Agreement. Company agrees to provide NIAID (DCR) any updated version of the IB, with the SOC, within fifteen (15) days of issuance. Company will send the IB and SOC to the NIAID (DCR) to the attention of the NIAID contact for regulatory matters identified in Article 26. NIAID (DCR), through the SDMC, will distribute the IB to the Clinical Research Sites. NIAID (DCR) will address requests for IBs, including updated versions and SOCs, to:

(b)(6)
Pfizer Inc.
(b)(6)
New York, NY (b)(6)
E-mail: (b)(6)

8. PROTOCOL DEVELOPMENT AND REGISTRATION

8.1 The Parties agree that enrollment in the Clinical Trial will not start until the version of the

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Protocol to be used has been reviewed in advance by Company, accepted by the Protocol Team, approved by the relevant IRB(s)/IEC(s) and NIAID (DCR) in writing, submitted to the FDA/HA, and any clinical hold issues have been responded to satisfactorily.

8.2 The Parties agree that any alteration in or amendment to the Protocol must be accepted by the Protocol Team, approved in writing by the relevant IRB(s)/IEC(s) and NIAID (DCR), and submitted to the FDA/HA prior to such alteration or amendment becoming effective.

(b)(4)

8.3 **Protocol Registration.** All NIAID (DCR)-sponsored network protocols which include the informed consent must meet all federal mandates as well as NIAID (DCR) requirements to ensure the welfare of Human Subjects in the Clinical Trial.

Each Clinical Research Site, prior to participating in any NIAID (DCR)-sponsored study, must submit its informed consent to the NIAID (DCR) or designee for review. (b)(4)

(b)(4)

(b)(4)

9. CASE REPORT FORM DEVELOPMENT

NIAID (DCR), through the SDMC, will be responsible for the development and subsequent revisions, if any, of the Case Report Forms with appropriate review and comment by the Protocol Team.

10. HUMAN SUBJECTS PROTECTION

10.1 NIAID (DCR) and Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The informed consent of each Human Subject participating in the Clinical Trial at a Clinical Research Site will be obtained prospectively using an informed consent process. The sample informed consent document will be reviewed in advance by Company representatives on the Protocol Team and shall be approved by NIAID (DCR) and all appropriate IRB(s)/IEC(s).

10.2 NIAID (DCR) and Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46, Protection of Human Subjects. Therefore:

10.2.1 NIAID (DCR) and Company will maintain the confidentiality of IPI, including PHI, collected under the Clinical Trial and protect the privacy of the individual Human Subjects unless disclosure is required by law.

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10.2.2 To the extent permitted by the informed consent forms and applicable laws, NIAID (DCR) and Company may inspect, but not copy, Human Subjects' medical records that might also include information not directly connected to this Clinical Trial. However, NIAID (DCR) and Company agree that this information will remain confidential and will not be used for any purpose other than confirmation of Clinical Trial data or to resolve study-related injury issues.

10.2.3 NIAID (DCR) and Company agree that neither Party will use, nor will it allow its contractors to use, IPI for any purpose not stated in the Protocol, without the consent of the other Party and local site IRB/IEC approval unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative. NIAID (DCR) will ensure that the Investigators do not use IPI for any purpose not stated in the Protocol and informed consent document without the written consent of both Parties and appropriate IRB/IEC approval, unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative.

10.2.4 NIAID (DCR) and Company agree to comply with the determinations of all IRB(s)/IEC(s) overseeing this research. NIAID will ensure that all Investigators adhere to all IRB/IEC determinations and requirements.

10.2.5 NIAID will ensure that biospecimens and data related to biospecimens provided to Company by NIAID, its awardees, sub-contractors, or Investigators during and after the Clinical Trial will be coded and will have all direct identifiers removed.

11. DATA COLLECTION, ANALYSIS AND MANAGEMENT

11.1 The Clinical Research Sites will be responsible for gathering the data and submitting it to the SDMC. The Protocol Team, which includes Company representatives, will be responsible for the scientific reporting of the data.

11.2 NIAID (DCR), through the SDMC, will have responsibility for the data management: collection, entry and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

11.3 It is the responsibility of both Company and the NIAID to protect the scientific integrity of the ACTIV 3 study. Doing so requires maintaining the study blind throughout the ACTIV-3 study unless the independent DSMB recommends otherwise. If the study product passes the initial futility assessment, no data will be unblinded until the target number of primary events is accrued or the DSMB recommends early termination. Following completion of primary analysis and unblinding of the data, the company will be provided with the data. If the study product does not pass the futility assessment, the DSMB may recommend unblinding of summary data on which the futility assessment was based, and, if so, the company will be provided the data. According to protocol,

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participants will continue to be followed through twelve (12) months and the blind will continue to be maintained for that data and the study participant and site clinical staff.

11.4 All data obtained from the Clinical Trial will be in the custody of the Investigator or the Clinical Research Site, as applicable, which produces such data. However, other than Company, its contractors and its designees, except for placebo arm Study data, any party wanting to review or use the data obtained from the Clinical Trial for purposes of seeking regulatory approval of the Study Product will obtain the prior written permission of Company.

11.5 Within four (4) weeks of database freeze or lock for the Study Product arm or other additional timepoints as agreed to by the Parties, the NIAID will authorize and ensure that the SDMC transfers to the Company a copy of the raw data and data analysis set related to the Study Product and matched control in a machine-readable format to be determined jointly by the Parties. If Company requires that the data be provided in a customized format(s), Company will pay for all costs associated with the customized data format(s).

11.6 Subject to the right of NIAID (DCR) and the Investigators to publish the data from this Clinical Trial as set forth in the Publications and Press Releases Section of this Agreement, Company has the right to utilize the data reports from this Clinical Trial in its possession for all legitimate business or regulatory purposes. NIAID (DCR) and/or Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA/HA and the Securities and Exchange Commission (SEC), for all legitimate public health, regulatory or business purposes. Except for information related to regulatory or safety issues or under emergency circumstances where it is not practicable to do so and to the extent permitted by law, NIAID (DCR) will not release information regarding the Clinical Trial to governmental organizations without prior notification to Company.

11.7 Company will be responsible for preparing the final Clinical Study Report in accordance with ICH E3, “Structure and Content of Clinical Study Reports” and will provide a copy of the Clinical Study Report to NIAID (DCR) and the University of Minnesota for review and comment prior to its finalization.

11.8 Given the nature of the SARS-CoV-2 pandemic, it is anticipated that novel genetic variants of the SARS-CoV-2 will evolve which may impact the potency and/or efficacy of the Study Product. The Parties agree to cooperate in good faith to evaluate the effects of these variants on the potency of the Study Product, including the sharing of any data that relates to the potency of the Study Product against these variants. The Company agrees to cooperate in good faith with NIAID to determine the potency of the Study Product against any variants that arise that have the potential to impact the efficacy of the Study Product at any of the global Clinical Research Sites. (b)(4)

(b)(4)

(b)(4) NIAID will share the data generated through this testing with the

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Company. NIAID has the ability to make measurements of blood levels of the SARS-CoV-2 nucleoprotein (NP) and is willing to measure levels of NP and levels of antibodies to SARS-CoV-2 Spike Protein and NP in samples from other Company studies.

12. PUBLICATIONS AND PRESS RELEASES

12.1 Any publications based on the results of the Clinical Trial and originating from NIAID (DCR) or the Investigators will conform to the latest version of the INSIGHT Publications Standard Operating Procedure. Unless requested otherwise by Company, NIAID (DCR) will acknowledge Company as the source of the Study Product in any NIAID (DCR) publication resulting from the Clinical Trial and will ensure that the Investigators do the same in their publications resulting from the Clinical Trial, and that Investigators accurately report any conflicts of interest in their publications.

12.2 Recognizing that employees of either Party may play an important role in the design, analysis and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the generally accepted customs pertaining to authorship. NIAID (DCR) will ensure that the Investigators include appropriate individuals from both Parties in their publications resulting from the Clinical Trial. For all publications relating to the Clinical Trial, each Investigator and Party will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors (ICMJE). All authors will have access to the relevant statistical tables, figures and reports required to develop the publication.

12.3 Each Party will provide, and NIAID (DCR) will ensure that the Investigators provide, a copy of any abstract or manuscript to the other Party prior to submission for publication with sufficient time for review and comment, as outlined in the INSIGHT Publications Standard Operating Procedure [Manuscripts: ten (10) days; Abstracts: five (5) days]. The publication or other disclosure may be delayed for up to thirty (30) additional business days for manuscripts and up to five (5) business days for abstracts, upon written request by either Party as necessary to preserve U.S. or foreign Patent or other intellectual property rights. Each Party agrees that, following the receiving Party's review of the manuscript and/or abstract for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish, present or use any Clinical Trial data provided that if the publication or presentation is not submitted by the Company, the Company may remove Company Confidential Information from such publication or presentation. If the Company requests redaction of its Confidential Information, the Company will make reasonable efforts to supply substitute non-confidential information in order to allow the publication to go forward. Notwithstanding the timelines described above, the Parties agree that expedient publication of the Clinical Trial results is necessary for the public good and the Parties agree to work in good faith to allow expeditious publication of the Clinical Trial results.

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12.4 Each Party will provide, and NIAID (DCR) will ensure that the Investigators provide, a copy of any proposed press release to the other Party for review at least five (5) business days in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish the press release. Each Party reasonably consider the other Party's requested revisions into their press releases.

13. CONFIDENTIAL INFORMATION

13.1 Either Party may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct the Clinical Trial. (b)(4)

(b)(4)

(b)(4) Each Party receiving Confidential Information agrees that any information so designated will be used by it only for the purposes of the Clinical Trial. Any Party may object to the designation of information as Confidential Information by the other Party.

13.2 Unless expressly provided otherwise, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA), 5 U.S.C. § 552, or other applicable laws and/or regulations to disclose the Confidential Information, except:

(i) NIAID (DCR) and Company may disclose Confidential Information to, in the case of NIAID, those contractors to which NIAID has delegated its obligation in connection with the conduct of Clinical Trial, Investigators, Clinical Trial site IRBs, Investigtors, and Protocol staff, in all cases to the degree necessary to conduct the Clinical Trial, and in the case of Company, to those of their representatives, agents, officers, grantees, contractors, consultants and employees (collectively for both NIAID and Company, "Agents") to the degree necessary to conduct the Clinical Trial. The Parties will ensure that their respective Agents maintain the confidentiality of Confidential Information in accordance with the terms of this Agreement.

(ii) Subject in each case to the provisions in this Agreement set forth in Section 12 (Publication and Press Releases) of this Agreement, a Party may publicly disclose information that is reasonably required by scientific standards for publication of the results of the Clinical Trial (including Clinical Trial methods and/or data) or

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any information that is necessary for other researchers to verify the results of the Clinical Trial.

(iii) A Party may publicly disclose information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Study Product.

(iv) A Party may disclose information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, or required to be disclosed by a court of competent jurisdiction or governmental authority, provided that the Party required to disclose provides the other Party with prompt written notice and an opportunity (if legally permissible) to obtain a protective order.

(v) (b)(4)

13.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. Current NIH policy requires that a brief synopsis, the enrollment status and study results for all NIH-funded clinical trials be posted in the ClinicalTrials.gov registry of clinical studies, available through the NIH website. NIAID (DCR) shall be responsible for submitting information to ClinicalTrials.gov after review of information related to the Study Product by Company's representative on the Protocol Team, provided that the Company may remove Company Confidential Information from such posting to ClinicalTrials.gov. If the Company requests redaction of its Confidential Information, the Company will make reasonable efforts to supply substitute non-confidential information in order to allow such posting to go forward.

13.4 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given an opportunity to seek a court order to enjoin from disclosure.

13.5 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above, or five (5) years after the expiration or termination date of this Agreement, provided, however, that NIAID agrees to keep confidential and not use, except as permitted herein, all Company Know-How until such Company Know-How is no longer Conflidential Information. Either Party may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

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14. INTELLECTUAL PROPERTY

14.1 Ownership of any invention made solely or jointly by NIAID (DCR), the Clinical Research Sites and Investigators, or other NIAID (DCR) contractors or grantees as a consequence of conducting the Clinical Trial and involving the Study Product, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party claims by virtue of this Agreement any right, title, or interest in or to any issued Patents or pending Patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any right, license or obligation to license any Patent, pending Patent application, or other intellectual property owned by Company to NIAID (DCR) with respect to the Study Product, other than the limited right to use the Study Product for the performance of the Protocol in accordance with the terms of this Agreement.

14.2 **NIAID (DCR) Intellectual Property.**

14.2.1 The Government will retain title to any Patent or other intellectual property rights in inventions made solely by NIAID (DCR) employees in the course of the Clinical Trial.

14.2.2 NIAID (DCR) agrees to notify Company of any such Invention and is willing to disclose it to Company under an appropriate confidentiality agreement. Company may apply for exclusive or non-exclusive license rights to any patentable Invention made solely by NIAID (DCR) employees that might arise during the clinical research and the NIH will consider Company's application for a license consistent with 37 C.F.R. Part 404.

14.3 **Company Intellectual Property.** Company will retain title to any Patent, pending Patent application, or other intellectual property rights in Inventions made by its employees during the course of the Clinical Trial.

14.4 **Clinical Research Site/Investigator Intellectual Property.** This Agreement does not grant or preclude intellectual property rights, including, but not limited to, Inventions made by INSIGHT, the Investigators, or other Government contractors or grantees during the course of the Clinical Trial. Company may enter into a separate agreement with the Clinical Research Sites or Investigators regarding intellectual property rights that do not interfere with the conduct of this Clinical Trial or contradict the terms of this Agreement.

14.5 **Joint NIAID-Company Intellectual Property.**

14.5.1 NIAID and Company will have joint intellectual property rights in Inventions made jointly by their employees during the course of the Clinical Trial.

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14.5.2 Each Party agrees to notify the other Party of any such Invention. Company may apply for exclusive or non-exclusive license rights to any patentable Invention made jointly by NAID and Company employees that might arise during the clinical research and the NIH will consider Company's application for a license consistent with 37 C.F.R. Part 404.

14.5.3 The Parties agree to negotiate in good faith the roles and responsibilities between the Parties relating to the preparation, filing, prosecution, issuance, maintenance and enforcement of any such Invention and the allocation of costs between the Parties with respect to such activities.

15. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

16. LIABILITY, INDEMNIFICATION AND INSURANCE

16.1 **Liability.** Activities carried out under this Agreement are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) as implemented under the amended declaration, "Public Readiness and Emergency Preparedness Act Coverage for medical countermeasures against COVID–19," issued on March 17, 2020 (85 Federal Register 15198). The PREP Act provides immunity from liability claims against manufacturers, distributors, program planners and other qualified persons ("Covered Persons") arising from the administration and use of covered countermeasures, as specified in a declaration by the Secretary of HHS ("Secretary") [See section 319F-3 of the Public Health Service Act (42 U.S.C. §247d-6d)]. The exception to this immunity is acts of willful misconduct by the Covered Persons. The Study Product is considered a drug to treat, prevent or mitigate COVID-19, and as such is a covered countermeasure under the Secretary's declaration. Informed consent forms used in the Clinical Trial will include a sufficient description of the PREP Act for participants to understand that all Covered Persons have immunity from liability under the PREP Act, and what compensation may be available under the PREP Act Countermeasure Injury Compensation Program [See section 319F-4 of the Public Health Service Act (42 U.S.C. §247d-6e)]. To the extent that PREP Act coverage is not available, each Party shall be liable for any loss, claim, damage or liability that it incurs as a result of its direct activities under this Agreement, except that NIAID (DCR), as an agency of the U.S. Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171. (b)(4)

(b)(4)

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16.2 **Indemnification.** NIAID is prohibited under the Anti-Deficiency Act, 31 U.S.C. § 1341 from indemnifying Company for any losses incurred as a result of this Clinical Trial. Each Party will be liable for the losses, claims, damages or liabilities that it incurs as a result of its activities under this Agreement. Company's right and obligation to defend NIAID and Company's control over the defense and settlement of any claim against NIAID will be subject to the consent of NIAID and the Department of Justice.

To the extent that PREP Act coverage is not available, Company will defend, indemnify and hold harmless the Government's grantees and contractors and their respective agents and employees ["Indemnitee(s)"] from any and all liabilities, damages, losses, claims, action, suits and expenses, including attorneys' fees and court costs (collectively "Claims") to the extent caused by (b)(4) (b)(4) the administration or use of the Study Product during the course of the Clinical Trial, provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if each of the following conditions is met:

16.2.1 The Claim was not proximately caused by the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, any written instructions from Company, and this Agreement.

16.2.2 The Claim was not caused by the gross negligence, recklessness or willful misconduct of any Indemnitee, provided that any action properly taken by the Indemnitee in compliance with the Protocol or written instructions from Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if a Claim is jointly caused by the negligence of any Indemnitee or Clinical Trial Site, then Company will provide defense and indemnification to the extent the Claim was caused by (b)(4) (b)(4) in the administration of the Study Product.

16.2.3 Company is promptly notified of the Claim, provided that the failure to give such notice will not abrogate or diminish Company's defense and indemnity obligation if Company has or receives knowledge of the existence of the Claim by any other means or if such failure does not prejudice Company's ability to defend the Claim.

16.2.4 Company will have sole control over the defense and settlement of the Claim(s) directed against Company.

16.2.5 Company will have the right to select defense counsel and to direct the defense and settlement of the Claim(s) directed against Company.

16.2.6 Company will provide a diligent defense against and/or settlement of any Claims for which defense and indemnification are provided under this Agreement whether such Claims are rightfully or wrongfully made. Company will have the right to settle such Claims, at Company's sole expense and in Company's sole

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discretion. Indemnitee(s) will fully cooperate, at Company's expense, with Company and its legal representatives in the investigation and defense of any Claim for which defense and indemnification are provided under this Agreement.

16.2.7 The Indemnitee(s) will at all times have the right to fully participate in the defense of any Claim at their own expense and for their own account. If Company will, within a reasonable time after notice, fail to defend any Claim for which defense and indemnification are provided under this Agreement, the Indemnitee(s) will have the right, but not the obligation, to undertake the defense of and to compromise or settle the Claim on behalf, for the account, and at the risk of Company.

16.3 **Insurance.** Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the research related injury and indemnification obligations assumed under this Agreement. Upon request, Company will provide evidence of its insurance or self-insurance to NIAID (DCR).

17. DISPUTE RESOLUTION

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the dispute will be referred to the Director of DCR**,** NIAID (or his/her designee) and an appropriate authorized representative of Company for resolution. If the Director of DCR (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute through good faith negotiations within thirty (30) days, the dispute will be referred to the Director of NIAID (or his/her designee) and the authorized representative of Company. If the Director of NIAID (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute, either Party may pursue any and all administrative or judicial remedies that may be available.

18. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the other Party, enter into any contract, warranty, or representation as to any matter. Neither Party will be bound by the acts of the other Party.

19. NON-ENDORSEMENT

By entering into this Agreement, NIAID (DCR) does not directly or indirectly endorse any product or service provided, or to be provided, by Company. Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However,

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Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

20. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

21. SURVIVABILITY

The provisions (Clinical Research Sites and Investigators), (Investigational New Drug Application Sponsorship), (Supply, Distribution and Use of Study Product), (Human Subjects Protection), (Data Collection, Analysis and Management), (Publications and Press Releases), (Confidential Information), (Intellectual Property), (Liability, Indemnification and Insurance), (Dispute Resolution), (Independent Contractors), (Non-Endorsement), (Amendments) and this Section (Survivability) will survive the expiration or earlier termination of this Agreement.

22. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement. The provisions of this Agreement are severable and, in the event that any provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

23. ASSIGNMENT

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without the prior written consent to the other Party, provided, however, that Company may assign this Agreement, without NIAID's consent, to (a) an affiliate or (b) a person or entity that acquires all or substantially all of the business or assets of Company relating to the Study Product, whether by merger, reorganization, acquisition, sale or otherwise. An assignment to an affiliate under subsection (a) above shall not relieve Company of liability of its obligations hereunder. The terms and conditions of this Agreement shall be binding on and inure to the benefit of the permitted successors and assigns of the Parties.

24. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

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25. TERM AND TERMINATION

Unless terminated sooner in accordance with this Term and Termination Section, this Agreement will expire upon completion of all Clinical Trial activities and delivery of data analysis related to the Protocol and Study Product to the Company. The Parties may terminate this Agreement at any time by mutual written consent. Either Party may unilaterally terminate this Agreement at any time by giving written notice at least thirty (30) days prior to the desired termination date or immediately if such termination is based on safety concerns. The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically appropriate. (b)(4) (b)(4) (b)(4) In the event that Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution, Company must notify NIAID (DCR) within at least thirty (30) days of the dissolution.

26. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt), Portable Document Format (PDF) or via email followed by confirmational hard copies when requested.

For Company:

Global Product Development
Attn: (b)(6)
Pfizer Inc.
(b)(6)
New York, NY (b)(6)
E-mail: (b)(6)

With a copy to:

(b)(6)
(b)(6)

For NIAID (DCR):

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

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5601 Fishers Lane, Suite 6D
Rockville, MD 20892-9804
Phone: (b)(6)
Email:

For regulatory matters:

John Tierney, B.S.N., M.P.M
Clinical Research Oversight Manager
Office of Clinical Research Policy and Regulatory Operations
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9820
Rockville, MD 20852
Phone: (b)(6)
E-mail

For clinical matters:

Elizabeth Higgs, M.D.
Global Health Science Advisor
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9802
Rockville, MD 20852
Phone: (b)(6)
E-mail:

27. COUNTERPARTS

This Agreement may be executed in counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. Signatures to this Agreement transmitted by fax, by electronic mail in portable document (.pdf) format, or by any other electronic means intended to preserve the original graphic and pictorial appearance of the Agreement, will have the same effect as physical delivery of the paper document bearing the original signature.

SIGNATURES BEGIN ON THE NEXT PAGE

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

DocuSigned by:
H. Clifford Lane
1D059F32682D4F7...

(Signature)

(b)(4) 2021

(Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

DocuSigned by:
(b)(4); (b)(6)
218044EA5D4C436...

(Signature)

(b)(4) 2021

(Date)

(b)(4); (b)(6)

Pfizer Inc.
(b)(6)
New York, NY (b)(6)

cc: (b)(4)

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CONFIDENTIAL DISCLOSURE AGREEMENT

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, and fully amending and replacing that certain Confidential Disclosure Agreement between NIAID and Pfizer, as defined below, (b)(4) the National Institute of Allergy and Infectious Diseases, including its divisions such as the Division of Acquired Immunodeficiency Syndrome ("DAIDS") (collectively, "NIAID"), a component of the National Institutes of Health ("NIH"), an agency of the United States (U.S.) Department of Health and Human Services ("HHS") and Pfizer Inc. ("Pfizer"), (each a "Party" and collectively, the "Parties"), intending to be legally bound (b)(4) (b)(4) agree that:

1. A Party ("Disclosing Party") may disclose information to the other ("Receiving Party") for the purpose of (b)(4) (b)(4) ("Purpose"). The Disclosing Parties are: NIAID (for clarity, including DAIDS) and Pfizer.

2. The information disclosed under this Agreement ("Confidential Information") is described as:

   For Pfizer: (b)(4) (b)(4)

   For NIAID (for clarity, including DAIDS): (b)(4) (b)(4)

3. The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its, and its affiliates', employees, grantees, consultants, contractors (b)(4) investigators from the AIDS Clinical Trials Group (ACTG) including the UCLA coordinating center, IQVIA, Inc., International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) including the University of Minnesota coordinating center, Cardiothoracic Surgical Trials Network (CTSN), Prevention and Early Treatment of Acute Lung Injury (PETAL), employees of National Heart, Lung, and Blood Institute (NHLBI) involved in the oversight and management of CTSN and PETAL, employees of the Foundation for the National Institutes of Health (FNIH) involved the ACTIV program, the U.S. Department of Veterans Affairs (VA), and the Indian Council of Medical Research (ICMR), to whom it is necessary to disclose the Confidential Information for the Purpose described above (collectively, "Representatives"), and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information.

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4. The Receiving Party's duties under this Agreement shall apply to any Confidential Information shared orally or in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its Representatives that has been clearly marked "Confidential." Oral disclosures must be reduced to writing, marked (b)(4)

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure, in the possession of the Receiving Party; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party, without reference to the information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes in writing the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return all Confidential Information received from the Disclosing Party, except that the Receiving Party (i) may retain in its confidential files one (1) copy of written Confidential Information for record purposes only (b)(4)
(b)(4)

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes (b)(4)
(b)(4) to disclose any of the Confidential Information, (b)(4)
(b)(4)

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8. (b)(4)

9.

10.

11. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for (b)(4) years from the Effective Date.

12. Notices or other communications required to be sent to NIAID under this Agreement shall be sent in writing and addressed to National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Rockville, MD 20852 (if in regards to (b)(4)

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(b)(4) to the attention of Workforce Operations, Communications and Reporting Branch, Division of AIDS, at the address noted above; and if in regards to (b)(4) to the attention of Wade Green, Technology Transfer & Intellectual Property Office, at the address noted above, Suite 6D; email: (b)(6) @niaid.nih.gov). Notices required to be sent to Pfizer under this Agreement shall be in writing and addressed to Pfizer Inc., (b)(6) New York, NY (b)(6) Attn: Business Development Contract Notice; with a copy (which will not constitute notice) to Pfizer Inc., (b)(6) (b)(6) New York, NY (b)(6) Attn: Chief Counsel; and an email to (b)(6) @pfizer.com.

13. This Agreement may be executed in any number of counterparts, (b)(4)

(b)(4)

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
5601 Fishers Lane, Suite 6D
Rockville, MD 20852

Authorized Signature:

DocuSigned by:
Wade Green
A2FB83D9211C4A8...

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date (Month/Day/Year): (b)(4) 2021

Pfizer Inc.
(b)(6)
New York, NY (b)(6)

Authorized Signature:

(b)(4); (b)(6)

Date (Month/Day/Year): (b)(4) 2021

CONFIDENTIAL DISCLOSURE AGREEMENT

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, the Division of Acquired Immunodeficiency Syndrome ("DAIDS"), National Institute of Allergy and Infectious Diseases ("NIAID"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS"), and **Merck Sharp & Dohme Corp.,** ("**Merck**"), (each a "Party" and collectively, the "Parties"), intending to be legally bound as of the date of the last signature hereto ("Effective Date"), agree that:

1. A Party ("Disclosing Party") may disclose information to the other ("Receiving Party") for the purpose of discussing a proposed research collaboration on Merck's MK-4482 for the treatment of COVID-19 ("Purpose"). The Disclosing Parties are: NIAID (DAIDS) and Merck.

2. The information disclosed under this Agreement ("Confidential Information") is described as: any and all information associated with, and required to evaluate, Merck's MK-4482 (EIDD2801) and any associated use in clinical trials.

3. The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its employees, grantees, consultants or contractors to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms of confidentiality and non-use at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of the requirements of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information of a like nature.

4. The Receiving Party's duties under this Agreement shall apply only to Confidential Information disclosed under this Agreement, whether in written, oral or other tangible form. Confidential Information in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked "Confidential." Any Party that fails to mark tangible information as "Confidential" may remedy such failure by notice to the other Party at any time during the effective period of this Agreement. Regarding oral disclosures, if a Party does not reduce oral Confidential Information to writing, the Party must verbally provide notice of the confidential nature of the oral disclosure at the time it is disclosed for oral Confidential Information to be considered confidential under this Agreement.

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public

domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure, in the possession of the Receiving Party, as demonstrated by the Receiving Party's written records; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality to the Disclosing Party (and such rightful receipt can be demonstrated in writing); (d) is hereafter independently developed by the Receiving Party, without reference to the Confidential Information received from the Disclosing Party (and such independent development can be demonstrated in writing); or (e) the Disclosing Party expressly authorizes in writing the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return all Confidential Information received from the Disclosing Party except that the Receiving Party may retain in its confidential files one (1) copy of written Confidential Information for record purposes only.

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required to disclose any of the Confidential Information, the Receiving Party shall provide the Disclosing Party with timely notice and, to the extent practicable, consult with the Disclosing Party prior to any disclosure, and shall reasonably cooperate with the Disclosing Party's efforts to seek confidential treatment of any Confidential Information to be disclosed, or to obtain a protective order narrowing the scope of disclosure. Confidential Information that is disclosed pursuant to such required disclosure shall remain otherwise subject to the confidentiality and non-use provisions set forth herein.

8. This Agreement is made under and shall be construed in accordance with Federal laws as applied by the Federal Courts in the District of Columbia, and constitutes the entire understanding between the Parties with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for three (3) years from the Effective Date.

9. Notices or other communications required to be sent to NIAID (DAIDS) under this Agreement shall be sent in writing and addressed to Workforce Operations, Communications, and Reporting Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Rockville, MD 20852. Notices required to be sent to Merck under this Agreement shall be in writing and addressed to (b)(6) (b)(6) Sr. Principal Scientist, Merck Sharp & Dohme, 351 N. Sumneytown Pike, North Wales, PA 19454; e-mail: (b)(6) @merck.com.

10. Each Party has caused this Agreement to be executed on its behalf in duplicate (each of which duplicate shall be deemed to be an original).

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

The Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
5601 Fishers Lane
Rockville, MD 20852

Authorized Signature:

Carl W. Dieffenbach -S

Digitally signed by Carl W. Dieffenbach -S
Date: 2020.07.16 08:54:07 -04'00'

Carl W. Dieffenbach, Ph.D.
Director

Date (Month/Day/Year):_____

Merck Sharp & Dohme Corp.

One Merck Drive
Whitehouse Station, NJ 08889

Authorized Signature:

(b)(6)

(b)(6)

(b)(6)

Date (Month/Day/Year): 15 July 2020

(b)(6)

July 14, 2020

CONFIDENTIAL DISCLOSURE AGREEMENT

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, the **National Institute of Allergy and Infectious Diseases** ("**NIAID**"), a component of the **National Institutes of Health** ("**NIH**"), an agency of the U.S. Department of Health and Human Services ("**HHS**"), and **Merck Sharp & Dohme Corp.** ("**Merck**") (each a "**Party**" and collectively, the "**Parties**"), intending to be legally bound as of the date of the last signature hereto ("**Effective Date**"), agree that:

1. A Party ("**Disclosing Party**") may disclose information to the other ("**Receiving Party**") for the purpose of discussions on a possible collaboration on a Phase 3 study of Merck's molnupiravir ("**Purpose**").

2. The information disclosed under this Agreement ("**Confidential Information**") is described as: information/data related to Merck's molnupiravir, and a list of NIAID sites that are primed and ready to participate in studies that would advance molnupiravir. Confidential Information shall also include, but is not limited to, inventions, know-how, ideas, procedures, formulations, compounds, biologics, designs, formulae, methods, techniques, financial projections and/or terms, software, developmental or experimental work, clinical or other programs, and plans for research and development of a Party.

3. The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its Affiliates, employees, grantees, consultants, components of NIH or contractors, including investigators from the AIDS Clinical Trials Group (ACTG), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Cardiothoracic Surgical Trials Network (CTSN), and Prevention and Early Treatment of Acute Lung Injury (PETAL); employees of National Heart, Lung, and Blood Institute (NHLBI) involved in the oversight and management of CTSN and PETAL; employees of the Foundation for the National Institutes of Health (FNIH) involved in the ACTIV program; the U.S. Department of Veterans Affairs (VA); and the Indian Council of Medical Research (ICMR), to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information. For purposes of this Agreement, "**Affiliate**" means an entity at least 50% owned by, under common ownership with, or which owns at least 50% of, Merck.

4. The Receiving Party's duties under this Agreement shall apply only to Confidential Information in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked

"Confidential." Oral disclosures must be reduced to writing, marked "Confidential" and sent to the Receiving Party's representative designated in Paragraph 9 within thirty (30) days after disclosure to be considered Confidential Information.

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure in the possession of the Receiving Party; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party, without reference to the information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes in writing the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return all Confidential Information received from the Disclosing Party except that the Receiving Party may retain in its confidential files one (1) copy of written Confidential Information for record purposes only.

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required to disclose any of the Confidential Information, the Receiving Party shall provide the Disclosing Party with timely notice and, to the extent practicable, consult with the Disclosing Party prior to any disclosure.

8. The Disclosing Party makes no representation or warranty, express or implied, as to the accuracy or completeness of the Confidential Information, and shall have no liability as to the accuracy or completeness of the Confidential Information on any basis (including, without limitation, in contract, tort, under applicable securities laws or otherwise). The Receiving Party will not make any claims whatsoever against the Disclosing Party for any omissions or errors included in the Confidential Information. The Disclosing Party shall have no liability or responsibility for any decisions made by the Receiving Party in reliance on any Confidential Information disclosed under this Agreement. The Disclosing Party expressly disclaims any express or implied duty to update, supplement or correct any Confidential Information disclosed hereunder.

9. The Parties acknowledge that a material breach of this Agreement by the Receiving Party may cause irreparable harm to the Disclosing Party and that no remedy at law may adequately compensate the Disclosing Party for such harm. The Disclosing Party shall have the right to seek injunctive relief or other equitable relief without prejudice to any other rights or remedies that the Disclosing Party may have for the material breach of this Agreement.

10. This Agreement is made under and shall be construed in accordance with Federal laws as applied by the Federal Courts in the District of Columbia, and constitutes the entire understanding between the Parties with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for five (5) years from the Effective Date.

11. Notices or other communications required to be sent to NIAID under this Agreement shall be sent in writing and addressed to Wade Green, Technology Transfer & Intellectual Property Office, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Suite 6D, Rockville, MD 20852; e-mail: (b)(6) @nih.gov. Notices required to be sent to Merck under this Agreement shall be in writing and addressed to (b)(6) (b)(6) Merck Sharp & Dohme, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033; e-mail: (b)(6) @merck.com.

12. Upon Merck's request, NIAID will omit the Merck name or trademark from any publication, press release, Executive Summary, or abstract, except as required by applicable law or regulation or to warn of a health risk. For the exceptions noted, NIAID shall provide Merck with an opportunity of review and comment prior to using the company name or trademark.

13. This Agreement may be signed in any number of counterparts, each of which shall be deemed an original, but all of which shall constitute one and the same instrument. Signatures to this Agreement may be provided by facsimile transmission or PDF file, which shall be deemed to be original signatures.

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
5601 Fishers Lane, Suite 6D
Rockville, MD 20852

Authorized Signature:

Wade W. Green -S

Digitally signed by Wade W. Green -S
Date: 2021.03.11 18:20:59 -05'00'

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date (Month/Day/Year): 11 March 2021

Merck Sharp & Dohme Corp.

2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Authorized Signature:

(b)(6)

AVP, Business Development

Date (Month/Day/Year): _____

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
5601 Fishers Lane, Suite 6D
Rockville, MD 20852

Authorized Signature:

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date (Month/Day/Year):_____

Merck Sharp & Dohme Corp.

2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Authorized Signature:

(b)(6)
Electronically signed by (b)(6)
Reason: Approved
Date: Mar 11, 2021 16:44 EST

Date (Month/Day/Year): Mar 11, 2021

AMENDMENT NO. 1
TO THE CONFIDENTIAL DISCLOSURE AGREEMENT

Subject to full execution, this Amendment No. 1 ("Amendment) is made effective as of April 28, 2021 ("Amendment Effective Date"), and is entered into by and between the **National Institute of Allergy and Infectious Diseases** ("**NIAID**"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services (HHS), and **Merck Sharp & Dohme Corp.** ("**Merck**"), (each a "Party" and collectively the "Parties").

WHEREAS, NIAID and Merck are parties to that certain Confidential Disclosure Agreement for the purpose of discussions on a possible collaboration on a Phase 3 study of Merck's molnupiravir, having an Effective Date of March 11, 2021, as amended, supplemented or otherwise modified by the Parties from time to time ("Agreement").

WHEREAS, NIAID and Merck desire to amend the Agreement to allow for the disclosure of Confidential Information to other U.S. Government agencies.

NOW, THEREFORE, NIAID and Merck hereby agree as follows:

1. Section 3 of the Agreement is hereby amended to the following:

   "3. The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its Affiliates, employees, grantees, consultants, components of NIH or contractors, including investigators from the AIDS Clinical Trials Group (ACTG), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Cardiothoracic Surgical Trials Network (CTSN), and Prevention and Early Treatment of Acute Lung Injury (PETAL); employees of National Heart, Lung, and Blood Institute (NHLBI) involved in the oversight and management of CTSN and PETAL; employees of the Foundation for the National Institutes of Health (FNIH) involved in the ACTIV program; the U.S. Department of Veterans Affairs (VA); and the Indian Council of Medical Research (ICMR), to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. The Parties agree that NIAID is permitted to disclose Confidential Information to other U.S. Government agencies. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information. For purposes of this Agreement, "**Affiliate**" means an entity at least 50% owned by, under common ownership with, or which owns at least 50% of, Merck."

2. Except as expressly modified by this Amendment, all other terms and conditions as set forth in the Agreement shall remain the same and in full force and effect. Each capitalized term used in this Amendment, but not defined herein shall have the meaning ascribed to such term in the Agreement.

3. This Amendment together with the Agreement constitutes the entire agreement between the Parties with respect to the subject matter described herein and therein, and constitutes and supersedes all prior agreements, representations and understandings of the Parties, whether written, oral or otherwise.

4. This Amendment may be executed in counterparts, each of which together shall be deemed an original, but all of which together shall constitute one and the same instrument. In the event that any signature is delivered by facsimile transmission or by e-mail delivery of a ".pdf" format data file, such signature shall create a valid and binding obligation of the Party executing (or on whose behalf such signature is executed) with the same force and effect as if such facsimile or ".pdf" signature page were an original thereof.

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IN WITNESS WHEREOF, the Parties have executed this Amendment No. 1 through their duly authorized representatives as of the Amendment Effective Date.

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
5601 Fishers Lane, Suite 6D
Rockville, MD 20852

Authorized Signature:

Wade W. Green -S Digitally signed by Wade W. Green -S
Date: 2021.04.28 12:27:22 -04'00'

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date (Month/Day/Year): 04/28/2021

Merck Sharp & Dohme Corp.

2000 Galloping Hill Road
Kenilworth, NJ 07033

Authorized Signature:

(b)(6)
(b)(6)

Date (Month/Day/Year): _____

IN WITNESS WHEREOF, the Parties have executed this Amendment No. 1 through their duly authorized representatives as of the Amendment Effective Date.

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
5601 Fishers Lane, Suite 6D
Rockville, MD 20852

Authorized Signature:

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date (Month/Day/Year):_____

Merck Sharp & Dohme Corp.

2000 Galloping Hill Road
Kenilworth, NJ 07033

Authorized Signature:

(b)(6)

Electronically signed by (b)(6)
(b)(6)
Reason: Approved
Date: Apr 28, 2021 13:45 EDT

(b)(6)

AVP, Business Development

Date (Month/Day/Year): April 28, 2021

CDA-NIAID Amendment LKR 98267

Final Audit Report 2021-04-28

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CONFIDENTIAL DISCLOSURE AGREEMENT

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, National Institute of Allergy and Infectious Diseases ("NIAID"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS"), Vir Biotechnology, Inc. ("Vir"), and GlaxoSmithKline LLC ("GSK") (each a "Party" and collectively, the "Parties"), intending to be legally bound as of the date of the last signature hereto ("Effective Date"), agree that:

1. A Party ("Disclosing Party") may disclose information to the other ("Receiving Party") for the purpose of (b)(4); (b)(3):35 U.S.C. § 209(a) (b)(4); (b)(3):35 U.S.C. § 209(a) ("Purpose"). The Disclosing Parties are: NIAID, Vir, and GSK.

2. The information disclosed under this Agreement ("Confidential Information") is described as: (b)(4); (b)(3):35 U.S.C. § 209(a)

3. The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its employees, investigators from the AIDS Clinical Trials Group (ACTG), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Cardiothoracic Surgical Trials Network (CSTNCTSN), Prevention and Early Treatment of Acute Lung Injury (PETAL), employees of National Heart, Lung, and Blood Institute (NHLBI) involved in the oversight and management of CTSN and PETAL, employees of the Foundation for the National Institutes of Health (FNIH) involved the ACTIV program, and the U.S. Department of Veterans Affairs (VA), consultants or contractors to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information.

4. The Receiving Party's duties under this Agreement shall apply to any Confidential Information shared orally or in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked "Confidential." Regarding oral disclosures of Confidential Information, if a Party does not reduce oral Confidential Information to writing, the Party must verbally provide notice of the confidential nature of the oral disclosure at the time it is disclosed for the oral Confidential Information to be considered confidential under this Agreement.

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5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure in the possession of the Receiving Party; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party, without reference to the information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return all Confidential Information received.

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required to disclose any of the Confidential Information, the Receiving Party shall provide the Disclosing Party with timely notice and, to the extent practicable, consult with the Disclosing Party prior to any disclosure.

8. This Agreement is made under and shall be construed in accordance with Federal laws as applied by the Federal Courts in the District of Columbia, and constitutes the entire understanding between the Parties with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for (b)(4) (b)(4) years from the Effective Date.

9. Notices or other communications required to be sent to NIAID under this Agreement shall be sent in writing and addressed to Technology Transfer & Intellectual Property Office, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Ste 6D Rockville, MD 20852. Notices required to be sent to Vir under this Agreement shall be in writing and addressed to Vir Biotechnology, Inc., 499 Illinois St., Suite 500, San Francisco, CA 94158 Attention: Head of Alliance Management, Attention: Head of Legal; email: (b)(6) @vir.bio. Notices required to be sent to GSK under this Agreement shall be in writing and addressed to (b)(6) GSK, 5 Moore Drive, Durham, 27709, USA; email: (b)(6) @gsk.com.

10. Each Party has caused this Agreement to be executed on its behalf in duplicate (each of which duplicate shall be deemed to be an original).

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Institute of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH)
5601 Fishers Lane, Ste 6D
Rockville, MD 20852

Authorized Signature:

Wade W. Green -S Digitally signed by Wade W. Green -S
Date: 2020.07.16 16:24:35 -04'00'

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date (Month/Day/Year): 16 July 2020

Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158

Authorized Signature:

(b)(6)

Name: (b)(6)
Title: (b)(6)

Date (Month/Day/Year): 16-Jul-2020

GlaxoSmithKline LLC
1250 South Collegeville Road, Collegeville, PA 19426, USA
Authorized Signature:

(b)(6)

Name: (b)(6)
Title: (b)(6)

Date (Month/Day/Year): 17-Jul-2020

DocuSign Envelope ID: 70049FD4-0D27-49AA-8E06-5190C8BD5640

IND SPONSOR: NIAID (DCR)

CLINICAL TRIAL AGREEMENT

BETWEEN

DIVISION OF CLINICAL RESEARCH (DCR), NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

&

Vir Biotechnology, Inc.

&

GlaxoSmithKline LLC

Based on

Protocol ACTIV3/INSIGHT014

A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of
the Safety and Efficacy of Investigational Therapeutics for
Hospitalized Patients with COVID-19
Short Title: Therapeutics for Inpatients with COVID-19 (TICO)

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The **National Institute of Allergy and Infectious Diseases ("NIAID")**, an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the **Division of Clinical Research ("DCR")** and **Vir Biotechnology ("Vir")**, located at 499 Illinois Street, Suite 500, San Francisco, CA 94158 and **GlaxoSmithKline** LLC ("**GSK**"), located at 1250 South Collegeville Road, Collegeville, PA 19426, USA, (Vir and GSK collectively the "**Company**"), (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial designated as Protocol **ACTIV3/INSIGHT014**, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)."

This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). NIAID (DCR) will conduct this Clinical Trial with a consortium of clinical trial networks under the leadership and coordination of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). Other participating networks include the AIDS Clinical Trials Group (ACTG) under the terms of their Award with NIAID, as well as the Prevention and Early Treatment of Acute Lung Injury (PETAL) and the Cardiothoracic Surgery Trial Network (CTSN) under the terms of their Awards from National Heart Lung Blood Institute (NHLBI), and the U.S. Department of Veterans Affairs (VA). In the event that any other Clinical Research Sites funded by NIAID are included in this Clinical Trial in order to complete enrollment, these sites will meet NIAID standards for clinical research sites conducting research sponsored by NIAID. The Clinical Research Sites and their respective Investigators are not parties to this Agreement.

This Agreement sets forth the terms and conditions under which this Clinical Trial will be conducted and managed.

Company and NIAID (DCR) agree as follows:

1. DEFINITIONS

The terms listed in this Section will carry the meanings indicated throughout this Agreement. To the extent that a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code ("U.S.C.") or the Code of Federal Regulations ("C.F.R."), the definition in the U.S.C. or C.F.R. will control.

"**ACTG**" means the AIDS Clinical Trials Group network sponsored and funded by NIAID in accordance with the terms of an Award.

"**Adverse Event**" or "**AE**" means the definition as stated in the Protocol.

"**Affiliate**" means, with respect to Company, (i) any legal entity of which the securities or other ownership interests representing fifty percent (50%) or more of the equity or fifty percent (50%) or more of the ordinary voting power or fifty percent (50%) or more of the

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general partnership interest are, at the time such determination is being made, owned, controlled, or held, directly or indirectly, by such legal entity; or (ii) any legal entity which, at the time such determination is being made, is controlling or under common control with, such legal entity. As used herein, the term "control," whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract, or otherwise.

"**Agreement**" means this Clinical Trial Agreement ("**CTA**"), all executed amendments and supplements to this Agreement, and all schedules, appendices and/or addenda to this Agreement.

"Award" means any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between a Government agency and the awardee, who may subcontract with the Clinical Research Sites.

"**CTSN**" means the Cardiothoracic Surgery Trials Network (CTSN) funded by NHLBI in accordance with the terms of an Award.

"**Case Report Form**" or "**CRF**" means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Clinical Research Sites**" means the clinical research sites designated as INSIGHT sites and any other sites described in the introductory paragraph where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Trial**" means a biomedical or behavioral research study of Human Subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, or devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. In this Agreement, Clinical Trial means the clinical trial for the Protocol.

"**Confidential Information**" means confidential scientific, proprietary, business and/or financial information, provided that Confidential Information does not include:

(a) Information that is in the public domain or subsequently enters the public domain through no fault of the receiving Party;

(b) Information that is presently known or becomes known to the receiving Party from its own independent sources, without restriction as to confidentiality or use, from a person having the legal right to disclose the data;

(c) Information that can be established by competent proof was already known and lawfully in the possession of the receiving Party at the time of the disclosure, without restriction as to confidentiality or use;

(d) Information that is independently created or compiled by the receiving Party without reference to or use of the Confidential Information and such independent development can be documented by receiving Party with written records;

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(e) Information that is reasonably required by scientific standards for publication of the final results of the Clinical Trial (including Clinical Trial methods and/or data) or any information that is reasonably necessary for other researchers to verify the final results of the Clinical Trial, excluding any Company background confidential information;

(f) Information that relates to safety associated with the production, handling, or use of the Study Product; or

(g) Information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, or required to be disclosed by a court of competent jurisdiction or governmental authority, provided that the Party required to disclose provides the other Party with prompt written notice and an opportunity (if legally permissible) to obtain a protective order.

"**Critical Event**" means any unanticipated study-related serious adverse event that is likely to cause or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity.

"**Data and Safety Monitoring Board**" or "**DSMB**" means an independent group of experts that advises NIAID (DCR) and the Investigators. The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (2) make recommendations to NIAID (DCR) concerning the continuation, modification, or termination of the Clinical Trial.

"**Effective Date**" means the date of the last signature of the Parties executing this Agreement.

"**Electronic Common Technical Document**" or "**eCTD**" means the standard format for electronic regulatory submissions as per 21 U.S.C. § 379k-1, "Electronic Format for Submissions," and as further described in FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," 80 Federal Register 26057 (2015).

"**FDA**" means the U.S. Food and Drug Administration.

"**Government**" means the Federal Government of the United States of America.

"**Health Authority**" or "**HA**" means any non-U.S. Health Authority used when the Clinical Trial is being conducted in whole or in part at a non-U.S. Clinical Research Site requiring the use of non-U.S. regulatory agencies.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. § 46.102(e)(1), a living individual about whom an Investigator conducting research:

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(a) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimen; or
(b) Obtains, uses, studies, analyzes or generates Identifiable Private Information or identifiable biospecimens.

"**ICH**" means the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Cited are:
ICH E3: "Structure and Content of Clinical Study Reports."
ICH E6: "Good Clinical Practice: Consolidated Guidance," published in the Federal Register, 83 Federal Register 8882 (2018). Also referred to as "FDA Good Clinical Practice Guidelines."

"**Identifiable Private Information**" or "**IPI**" about a Human Subject means private information from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**IND**" means an "**Investigational New Drug Application**," filed in accordance with 21 C.F.R. Part 312, under which clinical investigation of an experimental drug or biologic (Study Product) is performed in Human Subjects in the U.S., or intended to support a U.S. licensing action.

"**INSIGHT**" means the International Network for Strategic Initiatives in Global HIV Trials funded under combination of (1) a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI) and (2) an Award from NIAID to the University of Minnesota.

"**Institutional Review Board**" ("**IRB**") or "**Independent Ethics Committee**" ("**IEC**") means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects, and 21 C.F.R. Part 56, Subpart C: IRB Functions and Operations, as amended April 1, 2013, and other applicable regulations, an independent body comprising medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of the Human Subjects involved in a clinical trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**Invention**" means any invention or discovery that is or may be patentable or otherwise protectable under Title 35 of the U.S.C.

"**Investigator**" means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Study Product to a Human Subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, Investigator means the individual(s) identified as responsible for the conduct of the Clinical Trial at any of the participating Clinical Research Sites.

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"**Investigator's Brochure**" or "**IB**" means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Study Product, including animal screening, preclinical toxicology and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the Study Product or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Study Product.

"Leidos Biomedical Research" means the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory activities related to NIAID (DCR)'s clinical research. Leidos operates pursuant to a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI).

"**Office for Human Research Protections**" or "**OHRP**" means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"**Patent**" means any issued U.S. patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

"PETAL" means Prevention and Early Treatment of Acute Lung Injury, a clinical trials network funded by NHLBI in accordance with the terms of an Award.

"**Protected Health Information**" or "**PHI**," as defined in 45 C.F.R. Parts 160 and 164, under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), includes any *individually identifiable* health information. *Identifiable* refers not only to data that is explicitly linked to a particular individual; it also includes health information with data items which reasonably could be expected to allow individual identification.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV3/INSIGHT014, "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)" and any company/product specific associated appendices. The Protocol describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. The Agreement will be governed by the most recent version of the Protocol, and should the Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement, the terms of the Agreement will govern.

"**Protocol Team**" means the team responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. The Protocol Team will

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include the protocol chair (an Investigator), representatives from Company, other Investigators, representatives from NIAID (DCR), and the persons involved with statistical and data analysis for the Clinical Trial. Participation on the Protocol Team will be as agreed by the Parties and will take into account any special requirements of the Protocol design.

"**Regulatory Application**" or "**RA**" means an IND-equivalent, non-U.S. Regulatory Application, applicable when the Clinical Trial is being conducted in whole or in part at a non-U.S. clinical research site.

"**Serious Adverse Event** (SAE)" means the definition as stated in the Protocol.

"**Sponsor**" means, in accordance with the definition in 21 C.F.R. § 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with Study Product. The Office of Clinical Research Policy and Regulatory Operations within the NIAID Division of Clinical Research is the IND/RA holder and sponsor of record for this agreement. Additionally, in accordance with 21 C.F.R. § 312.52(a) and any applicable HA requirements, several sponsor responsibilities will be transferred to the University of Minnesota Statistical and Data Management Center and to Leidos Biomedical Research.

"**Statistical and Data Management Center**" or "**SDMC**" means the data management center at the University of Minnesota responsible for providing statistical and data management services for INSIGHT clinical trials, including the Clinical Trial that is the subject of this Agreement in accordance with the terms of a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI).

"**Study Product**" means, in accordance with 21 C.F.R. § 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301, *et seq*., Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended. In this Agreement, the anti-SARS-CoV-2 monoclonal antibody VIR-7831 is referred to as the Study Product.

"VA" means the U.S. Department of Veterans Affairs.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 Company acknowledges that NIAID and NHLBI fund the Clinical Research Sites under Awards, and therefore, the Clinical Research Sites have certain existing contractual or other legal obligations to NIAID and NHLBI.

2.2 Company will not provide any funding or material for any aspect of the Clinical Trial to any Clinical Research Site participating in the Clinical Trial without prior written notification to NIAID (DCR). In addition, subject to Section 14.4 of this Agreement,

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Company will not enter into any separate agreements, including, but not limited to, material transfer agreements, with the Clinical Research Sites or the Investigators at the Clinical Research Sites that interfere with the conduct of this Clinical Trial.

2.3 NIAID (DCR) hereby certifies that it did not and will not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:
(i) debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or
(ii) suspended by OHRP as a clinical research site under 45 C.F.R. Part 46.

2.3.2 Any person convicted of a felony under federal law for conduct:
(i) relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application (NDA), Biologics License Application (BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or
(ii) otherwise relating to the regulation of any drug product or medical device under the FDCA.

2.3.3 Any person performing services in connection with this Clinical Trial who has been disqualified as a clinical investigator under 21 C.F.R. § 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required by 21 C.F.R. § 312.53.

2.4 If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party immediately.

2.5 The Awards require that the Investigators at Clinical Research Sites conduct the Clinical Trial in accordance with applicable provisions of ICH E6: FDA Good Clinical Practice Guidelines, and requires that they comply with all applicable U.S., foreign government, state and local laws, regulations and guidelines.

2.6 Company agrees that this Protocol will be conducted only at sites as defined by NIAID (DCR) and collaborating networks. However, Company can conduct, at its own expense and under its own IND, additional clinical trials with the Study Product at non-NIAID funded sites (b)(4); (b)(3):35 U.S.C. § 209(a)
(b)(4); (b)(3):35 U.S.C. § 209(a)
(b)(4); (b)(3):35 U.S.C. § 209(a) Company agrees to inform NIAID (DCR) in writing of any other clinical trials it may support for the use of the Study Product that would compete with this Clinical Trial for the same Human Subject population.

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2.7 (b)(4)

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND/RA.** NIAID (DCR) will be responsible for the submission of an IND/RA covering the Protocol to the FDA/HA. The IND/RA will satisfy all of the requirements of the FDA/HA, and, as applicable, will comply with eCTD format requirements. Company agrees to provide all requested documents to NIAID (DCR) in eCTD format. (b)(4)
(b)(4)
(b)(4) NIAID (DCR) will provide a copy of all IND/RA submissions to Company at the time they are submitted to the FDA/HA. Any Confidential Information of another party will be removed.

3.2 NIAID (DCR) may delegate regulatory obligations to one or more third parties to facilitate NIAID's oversight, monitoring, and administration of the Clinical Trial at Clinical Research Sites outside of the United States. NIAID (DCR)'s third party delegate(s) will submit any clinical trial application and subsequent reports to all applicable HA's outside of the United States.

3.3 **Clinical Research Site Monitoring.** NIAID (DCR) or their designeee, will be responsible for Clinical Research Site monitoring in accordance with the clinical monitoring plan. Monitoring will be done in compliance with applicable provisions of the FDA/HA Good Clinical Practice Guidelines (ICH) (E6). NIAID (DCR) will communicate any Critical Event findings from clinical monitors to Company (b)(4)
(b)(4)

3.4 **Adverse Event Reporting.**

3.4.1 NIAID (DCR) will collect Adverse Event reports according to the procedure outlined in the Protocol and in timeframes consistent with 21 C.F.R. § 312.32..
(b)(4)

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(b)(4)

NIAID (DCR) will report all SAEs associated with the Study Product observed in this Clinical Trial to the Company (b)(4)
(b)(4)

3.4.2 NIAID (DCR) will assume responsibility for the reporting all unexpected SAEs associated with the Study Product observed in this Clinical Trial to the FDA/HAs and Company on a timely basis consistent with 21 C.F.R. § 312.32 and the Protocol. NIAID (DCR) will report other serious and non-serious adverse events to the FDA/HAs and to Company on a timely basis consistent with 21 C.F.R. § 312.33. Company agrees not to contact the Clinical Research Sites directly for information related to Adverse Events. Company shall contact the NIAID (DCR) Safety Office for information related to SAEs.

(b)(4)

3.4.3 As the manufacturer, Company will, in a timely manner consistent with FDA/HA requirements and during the term of this Clinical Trial, provide NIAID (DCR) with any information it now has or may obtain in the future regarding the safety and/or the toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial. NIAID (DCR) will promptly transmit that information to all Investigators. Such information shall be sent to:

NIAID Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
(b)(6)
Fax: 301-846-6224
Email: rchspsafety@mail.nih.gov

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3.5. (b)(4)

4. SAFETY MONITORING

Data and Safety Monitoring Board (DSMB). A NIAID DSMB will monitor this Clinical Trial as described in the Protocol. NIAID will notify Company in advance of any DSMB review. NIAID will provide recommendations derived from the DSMB to Company. (b)(4)

(b)(4)

5. FDA/HA MEETINGS/COMMUNICATIONS

5.1 With respect to any discussions with the FDA/HA involving data obtained from this Clinical Trial under NIAID (DCR)'s IND/RA, NIAID (DCR), in consultation with Company, will take the initiative in arranging meetings or conference calls with the FDA/HA. Formal meetings with the FDA/HA concerning the Clinical Trial design and/or data will be discussed and agreed upon in advance by Company and NIAID (DCR). Company will have the right to participate in all formal meetings with the FDA/HA. Company agrees not to contact the FDA/HA independently of NIAID (DCR) concerning this Clinical Trial. However, Company may contact the FDA/HA on separate product-related issues. NIAID (DCR) will provide Company with copies of all transmittal letters for IND/RA submissions, and formal questions and responses that have been submitted to the FDA/HA. Any Confidential Information of another party will be removed.

5.2 Company will promptly notify NIAID (DCR) of:

(a) Any FDA/HA correspondence related to the Protocol that is received by Company, or its Affiliates; and
(b) FDA/HA enforcement actions directed toward Company or its Affiliates, including, but not limited to, warning letters, seizures, or recalls; injunctions/consent decrees; rejection of regulatory submissions or withdrawal of approval for a product; and
(c) Criminal investigations; and
(d) Proceedings to debar Company or its Affiliates or individuals employed under a contract to Company and/or its Affiliates.

5.3 Company will also promptly notify NIAID (DCR) of any action taken by the FDA/HA regarding manufacturing of the Study Product that would impact the safety of Human Subjects in the Clinical Trial.

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6. SUPPLY, DISTRIBUTION AND USE OF STUDY PRODUCT

6.1 **Supply.** NIAID (DCR) shall provide Company with an estimate of the quantity of Study Product that will be required to complete the Protocol. Company will supply the Study Product to NIAID (DCR) without charge and in quantities and conditions sufficient to complete the Protocol and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Study Product. Company will be responsible for labeling the Study Product used in the Clinical Trial.

6.2 **Distribution.**

6.2.1 Company will ship the Study Product to a central distribution site(s) to be arranged by NIAID, or the Clinical Research Sites, as mutually agreed by the Parties. Company will provide specific storage and/or shipping instructions for the Study Product to NIAID (DCR), the central distribution site(s), and/or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. Company warrants that any packaging for hazardous material, provided by Company, meets Department of Transportation regulatory requirements for use at all Clinical Research Sites.

6.2.2 The Study Product must be received by the central distribution site(s) or Clinical Research Sites in usable condition and accompanied by (b)(4)

(b)(4)

6.2.3 If there is evidence that the Study Product that arrived at the central distribution site(s) or Clinical Research Sites has not been maintained according to the defined shipping instructions, or is potentially adulterated, NIAID (DCR) will contact Company to inform it of the condition of the received Study Product and to determine if the Study Product is usable or if it must be replaced. If the Study Product must be replaced, Company will replace it at no cost to NIAID (DCR), the central distribution site(s), or the Clinical Research Sites.

6.3 **Use.** NIAID (DCR) will not transfer the Study Product to parties other than the central distribution site(s) or the Clinical Research Sites, nor will NIAID (DCR) chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed in writing by the Parties. NIAID (DCR), pursuant to the Awards, will ensure that the Investigators: (i) use the Study Product only in accordance with the Protocol and for no other purpose; (ii) do not transfer the Study Product to any parties except Company, the central distribution site(s), or the Clinical Research Sites; and (iii) do not chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed to, in writing, by the Parties.

6.4 **Study Product Return.** Upon completion of the Protocol, NIAID (DCR), will ensure destruction or, at Company's request, return any unused Study Product to Company.

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6.5 **Warranty.** Company represents and warrants that the Study Product supplied meets the specifications (b)(4)

6.6 **Source.**

6.6.1 In the event Company elects to terminate its development of Study Product for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to NIAID (DCR) within ninety (90) days of discontinuation then Company will provide NIAID (DCR) with Study Product sufficient to complete the Clinical Trial in the manner described in the Protocol.

6.6.2 The Parties also agree that should this Agreement be terminated prior to completion of the Protocol, the Protocol will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol and Company will supply enough Study Product to complete the Protocol.

7. INVESTIGATOR'S BROCHURE (IB)

Company will provide a (b)(4) for all applicable components of the Study Product, and any later revisions and addenda (b)(4)
(b)(4)

Company will send the (b)(4) to the NIAID (DCR) to the attention of the NIAID contact for regulatory matters identified in Article 26. NIAID (DCR), through the SDMC, will distribute (b)(4) to the Clinical Research Sites. NIAID (DCR) will address requests for (b)(4) to:

(b)(6)
(b)(6)

Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158Phone: (b)(6)
E-mail: (b)(6) @vir.bio

8. PROTOCOL DEVELOPMENT AND REGISTRATION

8.1 The Parties agree that enrollment in the Clinical Trial will not start until the version of the Protocol to be used has been reviewed in advance by Company, accepted by the Protocol Team, approved by the relevant IRB(s)/IEC(s) and NIAID (DCR) in writing, submitted to the FDA/HAs, and any clinical hold issues have been responded to satisfactorily.

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8.2 The Parties agree that any alteration in or amendment to the Protocol must be accepted by the Protocol Team, approved in writing by the relevant IRB(s)/IEC(s) and NIAID (DCR), and submitted to the FDA/HA prior to such alteration or amendment becoming effective.

8.3 **Protocol Registration.** All NIAID (DCR)-sponsored network protocols which include the informed consent must meet all federal mandates as well as NIAID (DCR) requirements to ensure the welfare of Human Subjects in the Clinical Trial.

Each Clinical Research Site, prior to participating in any NIAID (DCR)-sponsored study, must submit its informed consent to the NIAID (DCR) or designee for review prior to submission to the IRB/IEC.

9. CASE REPORT FORM DEVELOPMENT

NIAID (DCR), through the SDMC, will be responsible for the development and subsequent revisions, if any, of the Case Report Forms with appropriate review and comment by the Protocol Team.

10. HUMAN SUBJECTS PROTECTION

10.1 NIAID (DCR) and Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The informed consent of each Human Subject participating in the Clinical Trial at a Clinical Research Site will be obtained prospectively using an informed consent process. The sample informed consent document may be reviewed in advance by Company and shall be approved by NIAID (DCR) and all appropriate IRB(s)/IEC(s).

10.2 NIAID (DCR) and Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46, Protection of Human Subjects. Therefore:

10.2.1 NIAID (DCR) and Company will maintain the confidentiality of IPI, including PHI, collected under the Clinical Trial and protect the privacy of the individual Human Subjects unless disclosure is required by law.

10.2.2 To the extent permitted by the informed consent forms and applicable laws, NIAID (DCR) and Company may inspect, but not copy, Human Subjects' medical records that might also include information not directly connected to this Clinical Trial. However, NIAID (DCR) and Company agree that this information will remain confidential and will not be used for any purpose other than confirmation of Clinical Trial data or to resolve study-related injury issues.

10.2.3 NIAID (DCR) and Company agree that neither Party will use, nor will it allow its contractors to use, IPI for any purpose not stated in the Protocol, without the

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consent of the other Party and local site IRB/IEC approval unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative. NIAID (DCR) will ensure that the Investigators do not use IPI for any purpose not stated in the Protocol and informed consent document without the written consent of both Parties and appropriate IRB/IEC approval, unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative.

10.2.4 NIAID (DCR) and Company agree to comply with the determinations of all IRB(s)/IEC(s) overseeing this research.

10.2.5 Biospecimens and data related to biospecimens provided to Company during and after the Clinical Trial will be coded.

11. DATA COLLECTION, ANALYSIS AND MANAGEMENT

11.1 The Clinical Research Sites will be responsible for gathering the data and submitting it to the SDMC. The Protocol Team, which includes Company representatives, will be responsible for the scientific reporting of the data.

11.2 NIAID (DCR), through the SDMC, will have responsibility for the data management: collection, entry and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

11.3 (b)(4); (b)(3):35 U.S.C. § 209(a)

11.4 All data obtained from the Clinical Trial will be in the custody of the Investigator or the Clinical Research Site, as applicable, which produces such data. However, other than Company, its contractors and its designees, any party wanting to review or use the data obtained from the Clinical Trial for purposes of seeking regulatory approval of the Study Product will obtain the prior written permission of Company.

11.5 (b)(4) or other additional timepoints as agreed to by the Parties, the NIAID will authorize the SDMC to transfer to the Company a copy of the raw data and the data analysis set related to the Study Product and matched control in a machine-readable format to be determined jointly by the Parties. If Company requires that the raw data and data analysis be provided in a customized format(s), Company will pay for all costs associated with the customized data format(s).

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11.6 Subject to the right of NIAID (DCR) and the Investigators to publish the data from this Clinical Trial as set forth in the Publications and Press Releases Section of this Agreement, Company has the right to utilize the data analysis, data reports and the raw data from this Clinical Trial in its possession for all legitimate business or regulatory purposes. NIAID (DCR) and/or Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA/HAs and the Securities and Exchange Commission (SEC), for all legitimate public health, regulatory or business purposes. Except for information related to regulatory or safety issues or under emergency circumstances where it is not practicable to do so and to the extent permitted by law, NIAID (DCR) will not release information regarding the Clinical Trial to governmental organizations without prior notification to Company.

11.7 NIAID (DCR), through its contractor, will be responsible for preparing the final Clinical Study Report in accordance with ICH E3, "Structure and Content of Clinical Study Reports."

12. PUBLICATIONS AND PRESS RELEASES

12.1 Any publications based on the results of the Clinical Trial and originating from NIAID (DCR) or the Investigators will conform to the latest version of the INSIGHT Publications Standard Operating Procedure. Unless requested otherwise by Company, NIAID (DCR) will acknowledge Company as the source of the Study Product in any NIAID (DCR) publication resulting from the Clinical Trial and will ensure that the Investigators do the same in their publications resulting from the Clinical Trial.

12.2 Recognizing that employees of NIAID and Company may play an important role in the design, analysis and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the International Committee of Medical Journal Editors ("ICMJE") recommendations pertaining to authorship. NIAID (DCR) will ensure that the Investigators include appropriate individuals from both Parties in their publications resulting from the Clinical Trial.

12.3 Each Party will provide, and NIAID (DCR) will ensure that the Investigators provide, a copy of any abstract or manuscript to the other Party prior to submission for publication with sufficient time for review and comment, as outlined in the INSIGHT Publications Standard Operating Procedure, e.g., Manuscripts: fifteen (15) business days; and Abstracts: five (5) business days. The publication or other disclosure may be delayed for up to thirty (30) additional business days for manuscripts and up to five (5) business days for abstracts, upon written request by NIAID or Company as necessary to preserve U.S. or foreign Patent or other intellectual property rights. Company agrees that, following the receiving Party's review of the manuscript and/or abstract for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish, or present any Clinical Trial data provided that if the publication or presentation is not submitted by the Company, the Company may remove Company Confidential

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Information from such publication or presentation. If the Company requests redaction of its Confidential Information, the Company will make reasonable efforts to supply substitute non-confidential information in order to allow the publication to go forward.

(b)(4)

12.4 Each Party will provide, and NIAID (DCR) will ensure that the Investigators provide, a copy of any proposed press release to the other Party for review at least five (5) business days in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish the press release, provided that the submitting Party will reasonably consider an incorporate the comments from the non-submitting Party(s) prior to release.

13. CONFIDENTIAL INFORMATION

13.1 Any Party under this Agreement may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct the Clinical Trial. The disclosing Party will place a confidentiality notice on all the Confidential Information. Oral disclosures should be reduced to writing and marked "Confidential" (b)(4) after disclosure to be considered Confidential Information. If a Party does not reduce oral Confidential Information to writing, the Party must verbally provide notice of the confidential nature of the oral disclosure at the time it is disclosed for the oral Confidential Information to be considered confidential under this Agreement. Each Party receiving Confidential Information agrees that any information so designated will be used by it only for the purposes of the Clinical Trial. Any Party may object to the designation of information as Confidential by the other Party.

13.2 Unless expressly provided otherwise, no Party hereunder will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA) after appropriate consultation and redaction of company prioprietary and commercially sensitive information as permitted by FOIA,
5 U.S.C. § 552, by the rules or regulations of the United States Securities and Exchange Commission or similar regulatory agency in a country other than the United States or of any stock exchange or listing entity, or other applicable laws and/or regulations to disclose the Confidential Information, except that NIAID (DCR) and Company may disclose Confidential Information to those of their representatives, agents, officers, grantees, contractors, consultants and employees (collectively, "Agents") to the degree necessary to conduct the Clinical Trial. The Parties will ensure that their respective Agents maintain the confidentiality of Confidential Information in accordance with the terms of this Agreement.

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13.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. Current NIH policy requires that a brief synopsis, the enrollment status and study results for all NIH-funded clinical trials be posted in the ClinicalTrials.gov registry of clinical studies, available through the NIH website. NIAID (DCR) shall be responsible for submitting information to ClinicalTrials.gov after review of information related to the Study Product by Company's representative on the Protocol Team, provided that the Company may remove Company Confidential Information from such posting to ClinicalTrials.gov. If the Company requests redaction of its Confidential Information, the Company will make reasonable efforts to supply substitute non-confidential information in order to allow such posting to go forward.

13.4 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given an opportunity to seek a court order to enjoin from disclosure.

13.5 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above, or (b)(4) years after the expiration or termination date of this Agreement. Either Party may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

14. INTELLECTUAL PROPERTY

14.1 Ownership of any invention made solely or jointly by NIAID (DCR), the Clinical Research Sites and Investigators, or other NIAID (DCR) contractors or grantees as a consequence of conducting the Clinical Trial and involving the Study Product, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research.Neither the Company nor NIAID (DCR) claims by virtue of this Agreement any right, title, or interest in or to any issued Patents or pending Patent applications owned or controlled by the Company or NIAID (DCR), respectively, as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by Company to NIAID (DCR) with respect to the Study Product, other than the limited right to use the Study Product for the performance of the Protocol in accordance with the terms of this Agreement.

14.2 NIAID (DCR) Intellectual Property.

14.2.1 The Government will retain title to any Patent or other intellectual property rights in inventions made by NIAID (DCR) employees in the course of the Clinical Trial.

14.2.2 NIAID (DCR) will notify Company of any inventions made by NIAID (DCR) employees during the conduct of the Clinical Trial involving the Study Product, to the extent such inventions relate to the Study Product (including without limitation any new

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uses of or improvements thereto) (collectively, "Inventions") and NIAID (DCR) agrees not file for intellectual property rights for such Inventions.

14.3 **Company Intellectual Property.** Company will retain title to any Patent or other intellectual property rights in Inventions made by its employees during the course of the Clinical Trial.

14.4 **Clinical Research Site/Investigator Intellectual Property.** This Agreement does not grant or preclude intellectual property rights, including, but not limited to, Inventions made by INSIGHT, the Investigators, or other Government contractors or grantees during the course of the Clinical Trial. Company may enter into a separate agreement with the Clinical Research Sites or Investigators regarding intellectual property rights that do not interfere with the conduct of this Clinical Trial or contradict the terms of this Agreement.

14.4 **Joint NIAID-Company Intellectual Property.** NIAID and Company will have joint intellectual property rights in Inventions made jointly by their employees during the course of the Clinical Trial.

15. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

16. LIABILITY, INDEMNIFICATION AND INSURANCE

16.1 **Liability.** (b)(4)

(b)(4)

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16.2 **Indemnification.** NIAID is prohibited under the Anti-Deficiency Act, 31 U.S.C. § 1341 from indemnifying Company for any losses incurred as a result of this Clinical Trial. Each Party will be liable for the losses, claims, damages or liabilities that it incurs as a result of its activities under this Agreement. Company's right and obligation to defend NIAID and Company's control over the defense and settlement of any claim against NIAID will be subject to the consent of NIAID and the Department of Justice.

To the extent that PREP Act coverage is not available, Company will defend, indemnify and hold harmless the Government's grantees and contractors and their respective agents and employees ("Indemnitee(s)") from any and all liabilities, damages, losses, claims, action, suits and expenses, including attorneys' fees and court costs (collectively "Claims") to the extent caused by the administration or use of the Study Product during the course of the Clinical Trial, provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if each of the following conditions is met:

16.2.1 The Claim was not proximately caused by the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, any written instructions from Company, and this Agreement.

16.2.2 The Claim was not caused by the gross negligence, recklessness, willful misconduct or breach of applicable law of any Indemnitee, provided that any action properly taken by the Indemnitee in compliance with the Protocol or written instructions from Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if a Claim is jointly caused by the negligence of any Indemnitee and the administration or use of the Study Product, then Company will provide defense and indemnification to the extent the Claim was caused by the administration of the Study Product.

16.2.3 Company is promptly notified of the Claim, provided that the failure to give such notice will not abrogate or diminish Company's defense and indemnity obligation if Company has or receives knowledge of the existence of the Claim by any other means or if such failure does not prejudice Company's ability to defend the Claim.

16.2.4 Company will have sole control over the defense and settlement of the Claim(s) directed against Company.

16.2.5 Company will have the right to select defense counsel and to direct the defense and settlement of the Claim(s) directed against Company.

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16.2.6 Company will provide a diligent defense against and/or settlement of any Claims for which defense and indemnification are provided under this Agreement whether such Claims are rightfully or wrongfully made. Company will have the right to settle such Claims, at Company's sole expense and in Company's sole discretion. Indemnitee(s) will fully cooperate, at Company's expense, with Company and its legal representatives in the investigation and defense of any Claim for which defense and indemnification are provided under this Agreement.

16.2.7 The Indemnitee(s) will at all times have the right to fully participate in the defense of any Claim at their own expense and for their own account. If Company will, within a reasonable time after notice, fail to defend any Claim for which defense and indemnification are provided under this Agreement, the Indemnitee(s) will have the right, but not the obligation, to undertake the defense of and to compromise or settle the Claim on behalf, for the account, and at the risk of Company.

16.3 **Participant Injury Attributable to the Clinical Trial**. Company will pay the reasonable cost of medical care required by Clinical Trial participants for illness or injury attributable to the Study Product. For purposes of this determination and Company's obligation under this Agreement, "attributable" means that the receipt of the Study Product and the Clinical Trial participant's illness or injury are reasonably related in time, and the illness or injury is more likely explained by the receipt of the Study Product than another cause.

The payment or offer of payment of any amount by Company on behalf of a participant or his or her healthcare insurer or other third party payer under this Section is not an admission of fault or liability by any one or more of (a) the United States Government or any agency thereof; (b) the Clinical Research Site or its affiliate organizations, or (c) Company, its employees or agents, and any such payment or offer of payment will not be considered a waiver of any defense or other legal right by any of the foregoing in any legal, administrative or similar proceeding.

16.4 **Insurance.** Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the research related injury and indemnification obligations assumed under this Agreement. Upon request, Company will provide evidence of its insurance or self-insurance to NIAID (DCR).

17. DISPUTE RESOLUTION

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute (b)(4) after notification thereof, the dispute will be referred to the Director of DCR, NIAID (or his/her designee) and an appropriate authorized representative of Company for resolution. If the Director of DCR

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(or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute through good faith negotiations (b)(4) the dispute will be referred to the Director of NIAID (or his/her designee) and the authorized representative of Company. If the Director of NIAID (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute, either Party may pursue any and all administrative or judicial remedies that may be available.

18. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the other Party, enter into any contract, warranty, or representation as to any matter. Neither Party will be bound by the acts of the other Party.

19. NON-ENDORSEMENT

By entering into this Agreement, NIAID (DCR) does not directly or indirectly endorse any product or service provided, or to be provided, by Company. Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However, Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

20. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

21. SURVIVABILITY

The provisions (Clinical Research Sites and Investigators), (Investigational New Drug Application Sponsorship), (Supply, Distribution and Use of Study Product), (Human Subjects Protection), (Data Collection, Analysis and Management), (Publications and Press Releases), (Confidential Information), (Intellectual Property), (Liability, Indemnification and Insurance), (Dispute Resolution), (Independent Contractors), (Non-Endorsement), (Amendments) and this Section (Survivability) will survive the expiration or earlier termination of this Agreement.

22. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement. The provisions of this Agreement are severable and, in the event that any provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

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23. ASSIGNMENT

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without prior written notification to the other Party. The terms and conditions of this Agreement shall be binding on and inure to the benefit of the permitted successors and assigns of the Parties.

24. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

25. TERM AND TERMINATION

Unless terminated sooner in accordance with this Term and Termination Section, this Agreement will expire upon completion of all Clinical Trial activities and data analysis related to the Protocol and Study Product. The Parties may terminate this Agreement at any time by mutual written consent. Either Party may unilaterally terminate this Agreement at any time by giving written notice (b)(4) days prior to the desired termination date. The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol, and Company will supply enough Study Product to complete the Clinical Trial. In the event that Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution, Company must notify NIAID (DCR) within (b)(4) of the dissolution.

26. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt) or via facsimile followed by confirmational hard copies sent via international courier when it is necessary to receive or deliver documents within a very short period of time, e.g., less than one (1) day.

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For Company:

Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158
Email: (b)(6) @vir.bio

For regulatory matters:

(b)(6)
(b)(6)

Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158
Email: (b)(6) @vir.bio
Phone:

For technical matters:

(b)(6) (b)(6)

Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158
Email: (b)(6) @vir.bio
Phone:

For SAE forwarding:

GSK Case Management Group mail box: SAE Forms/Information should be forwarded to GSK via email preferably at (b)(6) @gsk.com or alternatively faxed to +44(0)208 754 7822 if email is unavailable.

For NIAID (DCR):

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
5601 Fishers Lane, Suite 6D
Rockville, MD 20892-9804
Phone: (b)(6)
Email: (b)(6) @niaid.nih.gov

For regulatory matters:

John Tierney, R.N., M.P.M
Clinical Research Oversight Manager
Office of Clinical Research Policy and Regulatory Operations
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9820

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Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

For clinical matters:
Elizabeth Higgs, M.D.
Global Health Science Advisor
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9802
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

27. COUNTERPARTS

This Agreement may be executed in counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. Signatures to this Agreement transmitted by fax, by electronic mail in portable document (.pdf) format, or by any other electronic means intended to preserve the original graphic and pictorial appearance of the Agreement, will have the same effect as physical delivery of the paper document bearing the original signature.

SIGNATURES BEGIN ON THE NEXT PAGE

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

(b)(6)

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(Signature) (Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6)

21-Aug-2020

(Signature) (Date)

(b)(6) (b)(6)

Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158

(b)(6)

21-Aug-2020

(Signature) (Date)

(b)(6) (b)(6)

GlaxoSmithKline, LLC
1250 South Collegeville Road
Collegeville, PA 19426

cc: Principal Investigators, Clinical Research Sites

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AMENDMENT NO. 1
TO
CLINICAL TRIAL AGREEMENT

This 1st Amendment (NIAID Ref. No. 2020-1030-1) to Clinical Trial Agreement (NIAID Ref. No. 2020-1030) is made as of the date of the last authorized signature by and between Vir Biotechnology ("Vir"), GlaxoSmithKline LLC ("GSK"), and The National Institute of Allergy and Infectious Diseases ("NIAID"), an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the Division of Clinical Research ("DCR"). Vir and GSK collectively is referred to herein as the "Company". Each of Company and NIAID may be referred to herein as a "Party" or together as "Parties."

WHEREAS, Vir, GSK and NIAID entered into a Clinical Trial Agreement, dated August 27, 2020 (the "Agreement") for the conduct of the clinical trial designated as Protocol ACTIV3/INSIGHT014, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)" ; and

WHEREAS, the Parties desire to amend the Agreement as set forth herein;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, and intending to be legally bound, the Parties hereto agree as follows:

1. Definitions. All terms used in this Amendment and not otherwise defined herein shall have the same meanings ascribed to them in the Agreement.

2. Amendments:

   a. The definition of "Statistical and Data Management Center" or "SDMC" is deleted in its entirety and is replaced with the following:

   "**Statistical and Data Management Center**" or "**SDMC**" means the center at the University of Minnesota responsible for providing statistical and data management services for INSIGHT clinical trials, including the Clinical Trial that is the subject of this Agreement in accordance with the terms of a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI).

   b. The following definition of "SDMC Subcontractor" is added to the Agreement:

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c. Section 2.6 is deleted in its entirety and is replaced with the following:

2.6. Company agrees that this Protocol will be conducted only at sites as defined by NIAID (DCR), the SDMC, and collaborating networks. However, Company can conduct, at its own expense and under its own IND, additional clinical trials with the Study Product at non-NIAID funded sites (b)(4) (b)(4) (b)(4) Company agrees to inform NIAID (DCR) in writing of any other clinical trials it may support for the use of the Study Product that would compete with this Clinical Trial for the same Human Subject population.

d. Section 6.1 is deleted in its entirety and is replaced with the following:

6.1. **Supply.** NIAID (DCR) and the SDMC shall provide Company with an estimate of the quantity of Study Product that will be required to complete the Protocol. Company will supply the Study Product to NIAID (DCR) without charge and in quantities and conditions sufficient to complete the Protocol and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Study Product. Company will be responsible for labeling the Study Product used in the Clinical Trial.

e. Section 6.2 is deleted in its entirety and is replaced with the following:

6.2. **Distribution.**

6.2.1. Company will ship the Study Product to (b)(4) (b)(4) Company will provide specific storage and/or shipping instructions for the Study Product to NIAID (DCR), the SDMC, (b)(4) and/or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. Company warrants that any packaging for hazardous material, provided by Company, meets Department of Transportation regulatory requirements for use at all Clinical Research Sites.

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6.2.2. The Study Product must be received by the drug distribution depot(s) in usable condition and accompanied (b)(4) (b)(4)

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6.2.3. If there is evidence that the Study Product that arrived at the drug distribution depot(s) has not been maintained according to the defined shipping instructions, or is potentially adulterated, the SDMC or SDMC Subcontractor will contact Company to inform it of the condition of the received Study Product and to determine if the Study Product is usable or if it must be replaced. If the Study Product must be replaced, Company will replace it at no cost to NIAID (DCR), the drug distribution depot(s), or the Clinical Research Sites.

f. Section 6.3 is deleted in its entirety and is replaced with the following:

6.3. **Use.** NIAID (DCR) and the SDMC will not transfer the Study Product to parties other than the drug distribution depot(s) or the Clinical Research Sites, nor will NIAID (DCR) or the SDMC chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed in writing by the Parties. NIAID (DCR), pursuant to the Awards, will ensure that the Investigators: (i) use the Study Product only in accordance with the Protocol and for no other purpose; (ii) do not transfer the Study Product to any parties except Company, the drug distribution depot(s), or the Clinical Research Sites; and (iii) do not chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed to, in writing, by the Parties.

g. Section 6.4 is deleted in its entirety and is replaced with the following:

6.4. **Study Product Return.** Upon completion of the Protocol, NIAID (DCR) and the SDMC, will ensure destruction or, at Company's request, return any unused Study Product to Company (b)(4) (b)(4)

h. Section 11.7 is deleted in its entirety and is replaced with the following:

11.7. (b)(4) will be responsible for preparing the final Clinical Study Report in accordance with ICH E3, "Structure and Content of Clinical Study Reports" (b)(4) (b)(4) (b)(4)

3. All other terms and conditions of the Agreement shall remain unchanged.

SIGNATURES BEGIN ON NEXT PAGE

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IN WITNESS WHEREOF, each Party has caused this This 1st Amendment (NIAID Ref. No. 2020-1030-1) to Clinical Trial Agreement (NIAID Ref. No. 2020-1030) to be executed by its authorized representative.

ACCEPTED AND AGREED TO:

(b)(6)

(Signature) 10/20/2020 (Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6)

(Signature) 21-Oct-2020 (Date)

(b)(6) (b)(6)
Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158

(b)(6)

(Signature) 21-Oct-2020 (Date)

(b)(6) (b)(6)
GlaxoSmithKline, LLC
1250 South Collegeville Road
Collegeville, PA 19426

cc: Principal Investigators, Clinical Research Sites

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AMENDMENT NO. 2
TO
CLINICAL TRIAL AGREEMENT

This 2nd Amendment (NIAID Ref. No. 2020-1030-2) to Clinical Trial Agreement (NIAID Ref. No. 2020-1030) is made as of the date of the last authorized signature by and between Vir Biotechnology ("Vir"), GlaxoSmithKline LLC ("GSK"), and The National Institute of Allergy and Infectious Diseases ("NIAID"), an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the Division of Clinical Research ("DCR"). Vir and GSK collectively is referred to herein as the "Company". Each of Company and NIAID may be referred to herein as a "Party" or together as "Parties."

WHEREAS, Vir, GSK and NIAID entered into a Clinical Trial Agreement, dated August 27, 2020, as amended on October 21, 2020, (the "Agreement") for the conduct of the clinical trial designated as Protocol ACTIV3/INSIGHT014, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)" ; and

WHEREAS, the Parties desire to amend the Agreement as set forth herein;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, and intending to be legally bound, the Parties hereto agree as follows:

1. Definitions. All terms used in this Amendment and not otherwise defined herein shall have the same meanings ascribed to them in the Agreement.

2. Amendments:

   a. The following is added to the Agreement as Section 11.8:

   11.8. Given the nature of the SARS-CoV-2 pandemic, it is anticipated that novel genetic variants of the SARS-CoV-2 will evolve which may impact the potency and/or efficacy of the Study Product. The Parties agree to cooperate in good faith as set forth in 11.8.1 and 11.8.2.

   11.8.1. To share data on the effects of these variants on the potency of the Study Product in the Clinical Trial, on the same terms and conditions as agreed in the Agreement for the use of the Study Product.

   11.8.2. (b)(4)

(b)(4)

3. All other terms and conditions of the Agreement shall remain unchanged.

SIGNATURES BEGIN ON NEXT PAGE

IN WITNESS WHEREOF, each Party has caused this This 2nd Amendment (NIAID Ref. No. 2020-1030-2) to Clinical Trial Agreement (NIAID Ref. No. 2020-1030) to be executed by its authorized representative.

ACCEPTED AND AGREED TO:

(b)(6)

02|01|2021
(Signature) (Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6)

27-Jan-2021
(Signature) (Date)

(b)(6) (b)(6)

Vir Biotechnology, Inc.
499 Illinois Street, Suite 500
San Francisco, CA 94158

(b)(6)

27-Jan-2021
(Signature) (Date)

(b)(6) (b)(6)

GlaxoSmithKline, LLC
1250 South Collegeville Road
Collegeville, PA 19426

cc: Principal Investigators, Clinical Research Sites

DocuSign Envelope ID: (b)(4); (b)(6)

CONFIDENTIAL DISCLOSURE AGREEMENT

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, National Institute of Allergy and Infectious Diseases ("NIAID"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS"), NeuroRx, Inc. ("NeuroRx"), and Gilead Sciences, Inc. ("Gilead") (each a "Party" and collectively, the "Parties"), intending to be legally bound as of the date of the last signature hereto ("Effective Date"), agree that:

1. A Party ("Disclosing Party") may disclose information to another Party ("Receiving Party") for the purpose of planning, implementing, and conducting the ACTIV-3b clinical trial ("Purpose"). The Disclosing Parties are: NIAID, NeuroRx and Gilead.

2. The information disclosed under this Agreement ("Confidential Information") is described as:

   For NIAID: any and all information associated with the ACTIV-3b clinical trial that is disclosed to the other Parties for the Purpose

   For NeuroRx: any and all information associated with Aviptadil (VIP) that is disclosed to the other Parties for the Purpose

   For Gilead: any and all information and documents associated with remdesivir that is disclosed to the other Parties for the Purpose

3. A Receiving Party will not disclose the Confidential Information of a Disclosing Party to any person except its employees, consultants or contractors to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. NIAID may also disclose Gilead and NeuroRx confidential information to investigators from the AIDS Clinical Trials Group (ACTG), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Cardiothoracic Surgical Trials Network (CTSN), and Prevention and Early Treatment of Acute Lung Injury (PETAL) clinical trial networks; employees of National Heart, Lung, and Blood Institute (NHLBI) involved in the oversight and management of CTSN and PETAL; employees of the Foundation for the National Institutes of Health (FNIH) involved the ACTIV program; and the U.S. Department of Veterans Affairs (VA), and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. Receiving Party(ies) shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party(ies) uses to protect its own confidential information.

4. A Receiving Party's duties under this Agreement shall apply to any Confidential Information shared orally or in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked "Confidential." Oral disclosures must be reduced to writing, marked "Confidential" and sent to the Receiving Party's representative designated in Paragraph 9 within thirty (30) days after disclosure to be considered Confidential Information.

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure in the possession of the Receiving Party; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party, without reference to the Confidential Information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return, or destroy and certify such destruction in writing to the Disclosing Party, all Confidential Information received from the Disclosing Party, except that the Receiving Party may retain in its confidential files one (1) copy of written Confidential Information for record purposes only.

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required to disclose any of the Confidential Information, the Receiving Party shall provide the Disclosing Party with timely notice and, to the extent practicable, consult with the Disclosing Party prior to any disclosure.

8. It is acknowledged that nothing herein will be deemed to constitute, by implication or otherwise, the grant to any Party by the other of any license or other rights under any patent, patent application or other intellectual property right or interest. No Receiving Party shall seek any intellectual property protection regarding the Confidential Information of the Disclosing Party. A Party shall not use the name, trademark, service mark, or logo of another Party in any publicity, advertising, or other information without the prior written approval of such other Party.

9. This Agreement is made under and shall be construed in accordance with Federal laws as applied by the Federal Courts in the District of Columbia, and constitutes the entire understanding between the Parties with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the

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Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for three (3) years from the Effective Date.

10. Notices or other communications required to be sent to NIAID under this Agreement shall be sent in writing and addressed to Wade Green, Technology Transfer & Intellectual Property Office, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Ste 6D Rockville, MD 20852, email: (b)(6) @niaid.nih.gov. Notices required to be sent to NeuroRx under this Agreement shall be in writing and addressed to (b)(6) NeuroRx, Inc., 1201 N. Market Street, Suite 111, Wilmington, DE 19801, email: (b)(6) @neurorxpharma.com. Notices required to be sent to Gilead under this Agreement shall be in writing and addressed to Corporate Legal, 333 Lakeside Drive, Foster City, CA 94404, email: (b)(4) Fax: 650-522-5771.

11. NeuroRx and NIAID acknowledge that they are parties to that certain Confidential Disclosure Agreement having an Effective Date of November 18, 2020 (NIAID Reference#: 2020-1556), which remains in full force and effect, and that as between those two Parties to this Agreement, the provisions herein are intended to supplement and not replace the provisions thereof.

12. Each Party has caused this Agreement to be executed on its behalf in duplicate (each of which duplicate shall be deemed to be an original).

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Institute of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH)
5601 Fishers Lane, Ste 6D
Rockville, MD 20852

Authorized Signature:

DocuSigned by:
Wade Green
A2[illegible]1C[illegible]

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date : December 18, 2020 | 2:30:33 PST

NeuroRx, Inc.
1201 N Market St #111
Wilmington, DE 19801

Authorized Signature:

(b)(6)

(b)(6)

Title: (b)(6)

Date : December 18, 2020 | 4:53:07 PST

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Authorized Signature:

(b)(6)

(b)(6)

Title: (b)(6)

Date : December 18, 2020 | 8:54:21 PST

CLINICAL TRIAL MATERIAL SUPPLY AGREEMENT

THIS AGREEMENT (the "**Agreement**") is made as of July 13, 2020 (the "**Effective Date**").

1. PARTIES

1.1 **GILEAD SCIENCES, INC.**, a Delaware corporation with executive offices at 333 Lakeside Drive, Foster City, California 94404 ("GILEAD"); and

1.2 **THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES,** a National Institutes of Health agency with executive offices at 5601 Fishers Lane, Ste 6D, Rockville, MD 20852 ("RECIPIENT"); and

Each of GILEAD and RECIPIENT shall be referred to herein as a "Party" and, collectively, they shall be referred to as the "Parties".

2. BACKGROUND

2.1 GILEAD holds rights in the GILEAD STUDY DRUG (as hereinafter defined).

2.2 RECIPIENT desires to conduct the Clinical Trials ACTIV 3 and INSIGHT 013 (as hereinafter defined) utilizing the GILEAD STUDY DRUG and OTHER STUDY DRUG (as hereinafter defined).

2.3 GILEAD has agreed to supply RECIPIENT with certain quantities of GILEAD STUDY DRUG in accordance with this Agreement to enable RECIPIENT to carry out the Clinical Trials (as hereinafter defined).

2.4 Nothing contained in this Agreement shall be construed, by implication or otherwise, as a further commitment or obligation by either Party to enter into any further agreement or as the grant of a license to RECIPIENT to use GILEAD STUDY DRUG other than as expressly set forth in this Agreement. Nothing contained in this Agreement shall be construed, by implication or otherwise, as the grant of a license to GILEAD to use the OTHER STUDY DRUG.

3. DEFINITIONS

The following definitions shall apply in this Agreement:

3.1 **"Award"** - any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between a Government agency and the awardee, who may subcontract with the Clinical Research Sites.

3.2 **"Background Invention"** – any inventions conceived and first actually or constructively reduced to practice (as documented by competent written

records) before the Effective Date of this Agreement, or otherwise outside the scope of this Agreement.

3.3 **"Clinical Trials"** – the clinical studies to be conducted pursuant to the Protocol by Investigators at Study Centers.

3.4 **"Confidential Information"** – all information provided by the Disclosing Party (as hereinafter defined) to the Recipient Party, whether written, electronic, visual, or oral, and in any form including, without limitation, information relating to the Disclosing Party's proprietary drug, pricing data, financial data, information technology-related research and development plans, manuals, reports, patent applications, trade secrets and Inventions, including Background Inventions.

3.5 "**CRFs**" – the completed case report forms for the Clinical Trials.

3.6 **"Data"** – all results and data generated during the conduct of the Clinical Trials and all completed CRFs relating to the GILEAD STUDY DRUG or combination of GILEAD STUDY DRUG and OTHER STUDY DRUG, but shall not include Inventions, raw data, or patient records.

3.7 **"Disclosing Party"** – the Party which discloses its Confidential Information to the Recipient Party.

3.8 **"GILEAD STUDY DRUG"** – remdesivir supplied by GILEAD under the terms of this Agreement specifically for the Clinical Trial.

3.9 "**Health Authority**" – the United States Food and Drug Administration (or its successor agency) or comparable agencies in foreign countries performing similar functions.

3.10 **"Inventions"** – any invention or discovery that is or may be patentable or otherwise protected under 35 U.S.C., or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act, 7 U.S.C. §§ 2321 et seq.

3.11 "**Investigators**" – the principal investigators carrying out the Clinical Trials as designated from time to time by RECIPIENT.

3.12 "**OTHER STUDY DRUG**" – SARS-CoV-2 passive antibodies, including but not limited to SARS-CoV-2 hyper immunoglobulin and SARS-CoV-2 monoclonal antibodies.

3.13 "**Protocols**" – RECIPIENT Operation Warp Speed Protocols - A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19 (also known as ACTIV 3), and A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety,

Tolerability, and Efficacy of Anti-Coronavirus Hyperimmune Intravenous Immunoglobulin for the treatment of Hospitalized Patients with COVID-19 (also known as INSIGHT 013)."Protocol Teams" – the teams, under the direction of RECIPIENT, responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. The Protocol Teams will include the representatives from GILEAD, if they wish to participate, the principal Investigators, representatives from the RECIPIENT, and the persons involved with statistical and data analysis for the Clinical Trials.

3.14 **"Recipient Party"** – the Party which receives Confidential Information from the Disclosing Party.

3.15 **"Study Centers"** – the study centers for the Clinical Trials as designated by RECIPIENT from time to time.

4. COMMENCEMENT

This Agreement shall be effective as of the Effective Date.

5. INVESTIGATORS AND RESEARCH STAFF

5.1 Clinical Trials. RECIPIENT has designed the Clinical Trials. GILEAD wishes to provide the GILEAD STUDY DRUG for the Clinical Trials as per Article 6.2.

RECIPIENT will be responsible for contracting with Investigators and Study Centers for the conduct of the Clinical Trials.

5.2 Investigators. The Clinical Trials will be conducted by the Investigators at the Study Centers.

5.3 Contracting by RECIPIENT. RECIPIENT and the National Heart, Lung and Blood Institute (NHLBI) fund the Study Centers under Awards, and therefore, the Study Centers have certain existing contractual or other legal obligations to NIAID and NHLBI.

5.4 Obligations. RECIPIENT confirms that the obligations of Investigators described in this Agreement are consistent with the terms of the Awards in place for the conduct of the Clinical Trials.

5.5 Delegation of Duties by Investigators. Investigators may delegate duties and responsibilities to subinvestigators or research staff only to the extent permitted by the applicable Health Authority and regulations governing the conduct of clinical investigations. Investigators shall still be obligated for those duties and responsibilities delegated to third parties.

5.6 Compliance with Institutional Policies. RECIPIENT will require in each Award that Investigators comply with the policies and procedures of the organization(s) with which that Investigator is affiliated, including applicable financial policies. RECIPIENT will notify GILEAD within a reasonable time and in any event within five (5) days of any conflict of which it becomes aware between the applicable terms of this Agreement and any such policy or procedure in regard to any Investigator, and the Parties will attempt to reach an appropriate accommodation.

6. PROTOCOL REVIEW AND COMMENT/STUDY DRUG/SAFETY REPORTING

6.1 (b)(4)

6.2 GILEAD shall (b)(4) per agreed upon schedule (b)(4)

6.3 RECIPIENT shall report safety information to GILEAD as follows:

(a) GILEAD STUDY DRUG safety definitions used in this Agreement shall be interpreted in accordance with the Protocols and made a part hereof.

(b) RECIPIENT will collect safety reports according to the procedure outlined in the Protocol. RECIPIENT will be responsible for the management of safety data from the Clinical Trials and any associated regulatory reporting obligations for individual or periodic safety reports to appropriate authorities (including the FDA), Investigators, and applicable IRBs, in compliance with all applicable laws, rules and regulations, and the requirements of the IRBs.

(c) For any safety events collected according to the Protocol that meet all of the following criteria of (i) Serious (ii) Unexpected and (iii) Suspected Adverse Reaction, RECIPIENT will provide to GILEAD a completed copy of the IND safety report at the time the report is submitted to the FDA, RECIPIENT will provide follow up information to GILEAD at the time the

follow up safety report is submitted to FDA. The reporting will be completed in the timeframes consistent with 21 CFR 312.32.

(d) RECIPIENT will report all other safety events collected according to the Protocol not covered by 3.3.3 to the FDA and to GILEAD on a timely basis consistent with 21 CFR Part 312.33.

(e) RECIPIENT will alert GILEAD's Pharmacovigilance and Epidemiology (PVE) at the address below of any potential safety issues or any Protocol amendments or changes to the Informed Consent Form for the Clinical Trials arising from a safety concern associated with any GILEAD product within fifteen (15) calendar days of first becoming aware of such event.

(f) RECIPIENT will report in English all safety information as defined below, which includes, but is not limited to:

i. all Serious Adverse Events (SAEs) with respect to any GILEAD product no later than 15 calendar days of first becoming aware of such events; and

ii. (b)(4)

(g) All safety reports addressed to GILEAD must be sent to the attention of the GILEAD safety contact at:

Gilead Sciences, Inc.
Pharmacovigilance & Epidemiology
333 Lakeside Dr.
Foster City, CA 94404
Fax: 650.522.5477
Tel: 650.522.5114
E-mail: Safety_FC@gilead.com

(h) Upon GILEAD's request, and subject to any restrictions in applicable policies for the Clinical Trials, RECIPIENT will provide any additional information required to perform medical assessments of any safety information provided to GILEAD, including the provision of data in relation to blinded data if applicable. Upon GILEAD's request, and subject to any restrictions in applicable policies for the Clinical Trials, RECIPIENT will provide unblinding information for reports that are assessed as Serious and Unexpected Suspected Adverse Reactions (SUSARs). Unblinding information will be provided to Gilead either at the time of provision of the completed copy of the IND safety report to Gilead as per 6.3(c) above or upon request but within the timelines as defined in section 6.3(f)(i) above. RECIPIENT will provide GILEAD all reasonable assistance in providing any further information requested by GILEAD. GILEAD will send any

such request for additional information to RECIPIENT safety contact identified below:

NIAID Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
Email: rchspsafety@mail.nih.gov

(i) (b)(4)

(j) (b)(4)

(k) RECIPIENT will provide GILEAD with a copy of all reports submitted to government agencies that are related to the Clinical Trials and affect GILEAD or pertain to the GILEAD STUDY DRUG in any manner (including but not limited to the IND annual report), as well as any correspondence with such authorities related to the Clinical Trials and affect GILEAD or pertain to GILEAD STUDY DRUG in any manner.

(l) require in each Award that Investigators report safety information in accordance with this Article 6.3.

6.4 GILEAD represents and warrants that upon delivery to RECIPIENT the GILEAD STUDY DRUG will be in compliance with specifications and applicable laws and regulations relating to drugs intended for investigational use in humans.

6.5 (b)(4)

(b)(4)

7. STUDY CONDUCT

7.1 Sponsorship. RECIPIENT, not GILEAD, is the sponsor of the Clinical Trials. RECIPIENT will notify Investigators that they should not represent to any third party, including Clinical Trial subjects, that GILEAD is a sponsor of the Clinical Trials.

7.2 Regulatory. RECIPIENT is solely responsible for any and all safety reporting and regulatory obligations associated with the conduct of the Clinical Trials, including, but not limited to, obtaining and maintaining an Investigational New Drug application (IND) and submission and approval of relevant clinical trial applications if required for OTHER STUDY DRUG. RECIPIENT may delegate regulatory obligations to one or more third parties to facilitate RECIPIENT's oversight, monitoring, and administration of the Clinical Trials at Study Centers outside of the United States. RECIPIENT's third party delegate(s) will submit any clinical trial application and subsequent reports to all applicable regulatory authorities outside of the United States. (b)(4)

(b)(4)

7.3 Standards. RECIPIENT will, and will require in the Awards that Investigators, conduct the Clinical Trials in accordance with the Protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, and all applicable governmental laws, rules, and regulations.

7.4 IRB Approval. RECIPIENT will ensure, and require in the Awards, that the Clinical Trials is approved by and subject to continuing oversight by an appropriate Institutional Review Board (IRB) in the United States.

7.5 Informed Consent. RECIPIENT will ensure, and require in the Awards that, Investigators obtain informed consent for each Clinical Trial subject in accordance with 21 Code of Federal Regulations Part 50 in the United States and in accordance with ICH-GCPs or applicable regulations in other countries regarding informed consent. GILEAD shall be allowed to review and comment on the informed consent form solely as it relates to the use of the GILEAD STUDY DRUG and RECIPIENT shall include language provided by GILEAD related thereto.

7.6 HIPAA Authorization or Waiver. RECIPIENT will ensure, and require in the Award that, Investigators will obtain authorization or waiver of authorization, as applicable, for the use or disclosure of health information from each Clinical Trial subject in accordance with relevant laws and regulations and as contemplated under this Agreement.

7.7 Duration of Clinical Trials. RECIPIENT shall use reasonable efforts to complete the Clinical Trials in accordance with the Protocol. Notwithstanding the foregoing or any other provision to the contrary in this Agreement, RECIPIENT reserves the right to cancel or terminate the Clinical Trials at any time, in its sole discretion.

7.8 Compliance. The Parties shall comply with all applicable laws and regulations.

8. TERM AND TERMINATION

8.1 This Agreement shall expire upon the termination or expiration of the last Clinical Trial to terminate or expire, unless terminated earlier pursuant to the terms of this Agreement. RECIPIENT may cancel or terminate the Clinical Trials at any time, in its sole discretion.

8.2 This Agreement shall be immediately terminable by either Party in the event that the other Party commits a material breach of this Agreement that shall not have been remedied within thirty (30) days after receipt of written notice of such breach by such breaching Party from the nonbreaching Party, unless such material breach is not capable of remedy in which case the notice period shall not apply. In the event the breaching Party has not fully remedied such material breach within the thirty (30) day period following receipt of written notice as described in the foregoing sentence, but can show reasonable and continuing diligence to remedy such material breach, then the thirty (30) day time limit in the foregoing sentence shall be extended for a reasonable period of time, not to exceed ninety (90) days.

8.3 Either Party may terminate this Agreement at any time and for any reason with sixty (60) days prior written notice to the other Party. However, during such notice period, the Parties shall, as applicable, make good faith

efforts to resolve any and all issues related to the Party's election to so terminate.

8.4 The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trials, the Clinical Trials will be completed if medically appropriate. In that event, each enrolled human subject will be followed through the period outlined in the Protocol and (b)(4)

(b)(4)

8.5 Upon termination or expiration, RECIPIENT shall have no further obligations to GILEAD, except as set forth in those provisions that specifically survive the termination or expiration of this Agreement.

9. INTELLECTUAL PROPERTY

9.1 Ownership of any Invention conceived solely or jointly by RECIPIENT employees, the Study Centers and Investigators, or other RECIPIENT contractors or grantees as a consequence of conducting the Clinical Trials, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party acquires by virtue of this Agreement any right, title, nor interest in or to any issued Patents or pending patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by the GILEAD to the RECIPIENT.

9.2 NIAID Intellectual Property.

(a) The Government will retain title to any Patent, pending patent applications or other intellectual property rights in Inventions conceived solely by RECIPIENT employees in the course of the Clinical Trials.

(b) The RECIPIENT agrees to notify GILEAD of any RECIPIENT sole or joint Invention and to disclose it to GILEAD under an appropriate confidentiality agreement. GILEAD may apply for nonexclusive or exclusive license rights to any such patentable Invention made by RECIPIENT employees that might arise during the Clinical Trials and the RECIPIENT will consider the GILEAD's application for a nonexclusive or exclusive license consistent with 37 C.F.R. Part 404.

9.3 GILEAD Intellectual Property. GILEAD will retain title to any patents, pending patent applications, or other intellectual property rights in Inventions conceived by its employees during the course of the Clinical Trials.

9.4 Study Center/Investigator Intellectual Property.

(a) This Agreement does not grant any license or obligation to license any intellectual property of the Study Centers or preclude the creation of intellectual property rights, including but not limited to Inventions conceived by the Investigators or other RECIPIENT contractors or grantees during the course of the clinical research. GILEAD may enter into a separate agreement with the Clinical Research Site or Investigators, regarding intellectual property rights and confidentiality that do not interfere with the conduct of these Clinical Trials, contradict the terms of this Agreement or contradict the terms of the Award with RECIPIENT.

9.5 Joint RECIPIENT-GILEAD Intellectual Property. The RECIPIENT and GILEAD will have joint intellectual property rights in Inventions conceived jointly by their employees during the course of the clinical research. GILEAD may apply for a non-exclusive or exclusive license to the RECIPIENT rights in such Inventions in accordance with the 37 CFR 404.

10. CLINICAL STUDY STATUS AND RESULTS

10.1 GILEAD will be informed about the progress of the Clinical (b)(4) (b)(4) RECIPIENT shall also provide GILEAD with the final Clinical Study Report (CSR) immediately following submission to any Health Authorities. All reports provided under this section 10.1 are deemed to be RECIPIENT Confidential Information.

10.2 All medical records of Clinical Trial subjects under this Agreement shall remain the property of RECIPIENT or the Study Center, as applicable. RECIPIENT will require that Investigators record all Clinical Trial related Data from the original patient records onto the CRFs for the Clinical Trials. RECIPIENT shall retain a copy of all raw data recorded in the conduct of the Clinical Trials and all completed CRFs for the Clinical Trials and all other Clinical Trial documents in compliance with RECIPIENT's policies and all applicable laws. All data obtained from the Clinical Trials will be in the custody of the Investigator or the Study Center, as applicable, which produces such data. Without limiting Section 15, (b)(4)

(b)(4)

11. BIOLOGICAL SAMPLES

11.1 Collection, Retention and Use of Biological Samples. Specimens collected during the Clinical Trials as set forth in the Protocol ("**Biological Samples**") may include, without limitation, blood, serum, fluid and tissue biopsy samples collected from subjects enrolled in the Clinical Trials. Biological Samples further include, without limitation, any tangible material directly or indirectly derived from such blood, fluid or tissue samples, such as: genes, gene fragments, gene sequences, proteins, protein fragments, protein sequences, probes, DNA, RNA, cDNA libraries, plasmids, vectors, expression systems, cells, cell lines, organisms, antibodies or other biological substances; and any constituents, progeny, mutants, variants, derivatives, replications, reagents or chemical compounds thereof or derived therefrom. RECIPIENT shall only use the Biological Samples from Clinical Trial subjects in accordance with the Protocol and informed consent form.

11.2 RECIPIENT's Use of Biological Samples. RECIPIENT may receive quantities of Biological Samples from Study Centers, as set forth in the Protocol or informed consent form, for use in the research specified in the Protocol or informed consent form provided that such research complies with all applicable laws and regulations, including, but not limited to, patient privacy and informed consent laws. (b)(4)

(b)(4)

(b)(4)

12. CONFIDENTIALITY

12.1 Each of the Parties agrees that all Confidential Information of the Disclosing Party shall remain the sole and exclusive property of the Disclosing Party during the term of this Agreement and thereafter.

12.2 (b)(4)

(b)(4) Further, each Party agrees to take all reasonable precautions to prevent the disclosure by any of its employees, officers or agents of the Disclosing Party's Confidential Information to any third party or otherwise into the public domain. Each Party agrees as a Recipient Party that neither it, nor any employee or agent will be permitted to make any use of the Disclosing Party's Confidential Information except as permitted by this Agreement.

12.3 A Recipient Party may disclose the Disclosing Party's Confidential Information to the extent such disclosure is required to comply with applicable governmental regulations or to the extent ordered by a court exercising its right of authority over such Recipient Party provided that if a Recipient Party is required by such applicable law or court to make any such disclosure of Confidential Information, such Recipient Party will give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable best efforts to secure confidential treatment of the Confidential Information required to be disclosed.

(b)(4)

12.4 The provisions of this Section 12 do not apply to any Confidential Information which the Recipient Party demonstrates:

(a) was known to Recipient Party prior to receiving that information either directly or indirectly from Disclosing Party, as demonstrated by competent written records;

(b) is generally known to the public or which becomes generally known to the public through no act or omission on the part of Recipient Party; or

(c) is rightfully disclosed to Recipient Party at any time by a third party not a party to this Agreement without restriction.

12.5 Any and all of the Disclosing Party's Confidential Information received by Recipient Party, or any of its employees, officers or agents, in whatever form, including all copies or duplicates made or retained by Recipient Party, or any of its employees, officers or agents, shall be promptly returned to Disclosing Party upon written request by Disclosing Party, as the case may be, or disposed of in accordance with the written instructions of the Disclosing Party. The Recipient Party may retain one copy in its legal archives solely for purposes of monitoring its surviving obligations under this Agreement.

12.6 The obligations of this Section 12 shall terminate seven (7) years following termination or expiration of this Agreement.

13. REPRESENTATIONS, WARRANTIES AND CERTAIN COVENANTS

13.1 Each Party represents and warrants to the other Party that:

(a) it has legal power, authority and right to enter into this Agreement and to perform its respective obligations in this Agreement;

(b) it is not, as of the Effective Date, a party to any agreement, arrangement or understanding with any third party that prevents it from fulfilling any of its obligations under the terms of this Agreement; and

(c) it shall adhere to the terms of Attachment A.

13.2 Additionally, GILEAD represents and warrants to RECIPIENT that:

(a) (b)(4)

13.3 Additionally, RECIPIENT represents and warrants to GILEAD that:

(a) to its knowledge, the Study Center's personnel, facilities and patient population are adequate to perform the Study Center's obligations under the Protocol;

(b) it shall comply, and shall include provisions in each Award that the Study Center and Investigator shall comply with Health Authority reporting requirements, including those related to adverse event reporting, and all reporting requirements set forth in the Protocol and the PVA or as required by applicable laws;

(c) RECIPIENT will not permit any person or entity directly involved in the conduct of the Clinical Trials to use in any capacity the services of any person who has been debarred or disqualified by the Health Authority pursuant to the Generic Drug Enforcement Act of 1992 or any other equivalent or successor statutes, rules or regulations. RECIPIENT agrees and undertakes to promptly notify GILEAD in writing if it becomes aware that any such person or entity has been debarred or disqualified or proceedings have been initiated with respect to debarment or disqualification, whether such debarment or initiation of proceedings occurs during or after the performance of the Clinical Trials.

14. PUBLICITY AND PUBLICATION

14.1 Neither Party shall publicly disclose the terms of this Agreement without the prior written consent of the other Party, provided that RECIPIENT may disclose the terms on a need to know basis to the Study Centers or the Investigators to maintain their compliance with the obligations stated herein, as required, or as needed to comply with applicable laws.

14.2 With respect to any proposed presentation, publication, or abstract of the Data pursuant to this Section 15, the submitting party will submit to the

other Party a copy of the proposed presentation, publication, or abstract and the name of the scientific journal or forum to which the proposed presentation, publication, or abstract will be submitted at least (b)(4) (b)(4) for abstracts prior to the submission thereof for presentation, publication, or abstract. (b)(4) (b)(4)

15. GENERAL

15.1 No modification or amendment of this Agreement shall be effective unless made in writing and duly executed by an authorized signatory on behalf of each Party.

15.2 This Agreement constitutes the entire understanding among the Parties with respect to the subject matter hereof and supersedes all prior agreements and understandings between the Parties, whether written or oral, relating to the subject matter hereof.

15.3 Upon termination or expiration of this Agreement, Sections 7.2, 8.5, 9, 10, 11, 12, 13, 14, 15 and 16 shall continue in full force and effect.

15.4 This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

15.5 This Agreement shall not confer any rights or remedies upon any person or entity other than the Parties and their respective successors and permitted assigns.

15.6 This Agreement may be executed simultaneously in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

15.7 The section headings in this Agreement are inserted for convenience only.

15.8 Any term or provision of this Agreement that is invalid or unenforceable in any situation in any jurisdiction shall not affect the validity or enforceability of the remaining terms and provisions or the validation or enforceability of the offending term or provision in any other situation or in any other jurisdiction.

15.9 No failure on the part of either Party to exercise, and no delay in exercising, any right or remedy hereunder shall operate as a waiver thereof; nor shall any single or partial exercise of any right or remedy hereunder preclude any other or further exercise thereof or the exercise of any other right or remedy granted hereby or by any related document or by law.

15.10 Neither Party shall assign or transfer its interest in this Agreement or any portion thereof without the prior written consent of the other.

15.11 Each person signing this Agreement hereby certifies that he or she is duly authorized to execute this Agreement on behalf of the respective Party.

15.12 Neither Party shall be held liable to the other for failure of performance where such failure is caused solely by supervening conditions beyond the Party's reasonable control, including acts of God, civil disturbances, strikes, labor disputes, and lawful government action.

15.13 The Parties have participated jointly in the negotiation and drafting of this Agreement; therefore, no presumption or burden of proof shall arise favoring or disfavoring either Party based on authorship or drafting of any provision of this Agreement.

15.14 All notices or other communications required or permitted to be made or given hereunder shall be deemed so made or given when hand-delivered or sent in writing by registered or certified mail, postage prepaid and return-receipt requested, or by a recognized courier service, charges prepaid, and properly addressed to such other party as set forth below:

GILEAD:

(b)(6)
(b)(6)
333 Lakeside Drive,
Foster City, CA 94404

With copies to:

Gilead Sciences, Inc
333 Lakeside Drive
Foster City, California 94404
Attention: Clinical Legal
Facsimile: (b)(4)
Email: (b)(4)

and

RECIPIENT:

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
5601 Fishers Lane, Suite 6D
Rockville, MD 20892-9804
Phone: (b)(6)
Email: (b)(6) @niaid.nih.gov

For regulatory matters:
John Tierney, R.N., M.P.M
Clinical Research Oversight Manager
Office of Clinical Research Policy and Regulatory Operations
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9820
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

For clinical matters:
Elizabeth Higgs, M.D.
Global Health Science Advisor
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9802
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

IN WITNESS WHEREOF, the undersigned have executed this Agreement as the date first written above.

GILEAD SCIENCES, INC.

By: (b)(6)

(b)(6)

Date: 7/16/2020

THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

By: (b)(6)
H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

Date: 7/16/2020

#4037281v1

IND/RA SPONSOR: NIAID (DCR)

CLINICAL TRIAL AGREEMENT

For Clinical Trials Conducted at the National Institutes of Health

BETWEEN

DIVISION OF CLINICAL RESEARCH (DCR), NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

AND

GILEAD SCIENCES, INC.

Based on

Protocol ACTIV3b/INSIGHT015

A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of
the Safety and Efficacy of Investigational Therapeutics for
Hospitalized Patients with Acute Respiratory Distress Syndrome Associated with COVID-19
(TESICO)

Gilead No. CO-US-540-6090

The National Institute of Allergy and Infectious Diseases ("**NIAID**"), an institute of the National Institutes of Health (NIH), which is part of the United States Government Department of Health and Human Services (HHS), as represented by the **Division of Clinical Research** ("**DCR**") and Gilead Sciences, Inc. (together with its affiliates and subsidiaries, the "**Company**"), located at 333 Lakeside Drive, Foster City, California 94404 (individually referred to as the "**Party**" and collectively referred to as the "**Parties**") have agreed to cooperate in the conduct of a clinical trial designated as Protocol **ACTIV3b/INSIGHT015**, currently titled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with Acute Respiratory Distress Syndrome Associated with COVID-19 (TESICO)".

This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). NIAID (DCR) will conduct this Clinical Trial with a consortium of clinical trial networks under the leadership and coordination of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). Other participating networks include the AIDS Clinical Trials Group (ACTG) under the terms of their Award with NIAID, as well as the Prevention and Early Treatment of Acute Lung Injury (PETAL) and the Cardiothoracic Surgery Trial Network (CTSN) under the terms of their Awards from National Heart Lung Blood Institute (NHLBI), and the U.S. Department of Veterans Affairs (VA). In the event that any other Clinical Research Sites funded by NIAID are included in this Clinical Trial in order to complete enrollment, these sites will meet NIAID standards for clinical research sites conducting research sponsored by NIAID. The Clinical Research Sites and their respective Investigators are not parties to this Agreement.

This agreement sets forth the terms and conditions under which this clinical trial, with the aforementioned titled protocol (the "Protocol"), will be conducted and managed and for Company access to data/results from this Protocol.

The Company and the NIAID agree as follows:

1. DEFINITIONS

The terms listed in this Section have the meanings indicated throughout this Agreement. To the extent a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code (U.S.C.) or the Code of Federal Regulations (C.F.R.), the definition in the U.S.C. or C.F.R. will control.

"**ACTG**" means the AIDS Clinical Trials Group network sponsored and funded by NIAID in accordance with the terms of an Award.

"**Adverse Event**" (**AE)** means the definition contained in the Protocol.

"**Affiliates**" With respect to the Company, "Affiliates" means,

(i) any legal entity of which the securities or other ownership interests representing fifty per cent (50%) or more of the equity or fifty per cent (50%) or more of the ordinary voting power or fifty per cent (50%) or more of the general partnership interest are, at the time such determination is being made, owned, controlled or held, directly or indirectly, by such legal entity, or

(ii) any legal entity which, at the time such determination is being made, is controlling or under common control with, such legal entity.

As used herein, the term "control", whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract or otherwise.

"**Agreement**" means this Clinical Trial Agreement or "CTA", all executed amendments and supplements to this Agreement and all schedules to this Agreement.

"**Award**" means any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between a Government agency and the awardee, who may subcontract or otherwise coordinate with the Clinical Research Sites.

"**CTSN**" means the Cardiothoracic Surgery Trials Network (CTSN) funded by NHLBI in accordance with the terms of an Award.

"**Case Report Form**" **(CRF)** means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Certificate of Confidentiality**" (**CoC**) means a certificate issued by NIH pursuant to Section 301(d) of the Public Health Service Act (42 U.S.C. 241(d)), that protects the privacy of Human Subjects enrolled in the Protocol. With limited exceptions defined in 42 U.S.C. 241(d), the CoC protects from disclosure names or any information, documents or biospecimens containing ISI collected under the Protocol. Any investigator or institution not funded by NIH who receives a copy of ISI protected by a CoC issued by NIH, understand they are also subject to the requirements of subsection 301(d) of the Public Health Service Act and for ensuring that collaborators that are carrying out part of the research involving a copy of ISI protected by a CoC issued by NIH understand they are also subject to subsection 301(d) of the Public Health Service Act.

"**Clinical Research Sites**" means the clinical research sites designated as INSIGHT sites and any other sites described in the introductory paragraph where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Study Report**" in accordance with ICH E6 Section 1.13, is a written description of a Clinical Trial in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report. The Clinical Study Report contains information on results including reactogenicity, adverse events, immunogenicity and other clinical or laboratory observations made with respect to the intervention employed in conducting the Clinical Trial. A detailed description of the contents of a Clinical Study Report is found in ICH E3 "Structure and Content of Clinical Study Reports."

"**Clinical Trial**" means a biomedical or behavioral research study of Human Subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, or devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. In this Agreement, Clinical Trial means the clinical trial for the Protocol.

"**Confidential Information**" means confidential scientific, proprietary, business, or financial information provided by one Party to the other Party (including, without limitation, any

applicable Investigator's Brochure, clinical, preclinical or formulation data). For clarification, Confidential Information does not include:

(a) information that is within the public domain prior to the time of the disclosure by the disclosing Party to the receiving Party or thereafter becomes within the public domain other than as a result of disclosure by the receiving Party or any of its representatives in violation of this Agreement;

(b) information that was, on or before the date of disclosure in the possession of the receiving Party, as demonstrated by the receiving Party's independent records;

(c) information that is acquired by the receiving Party from a third party not under an obligation of confidentiality;

(d) information that is hereafter independently developed by the receiving Party, without reference to or use of the Confidential Information received from the disclosing Party, as shown by the receiving Party's written records; or

(e) information that the disclosing Party expressly authorizes, in advance and in writing, the receiving Party to disclose.

Notwithstanding the foregoing, Confidential Information of a Party may be disclosed by the other Party to those persons and to the extent reasonably required by:

(a) information that is reasonably required by scientific standards for publication of the results of the Clinical Trial (including Clinical Trial methods and/or data) or any information that is necessary for other researchers to verify the results of the Clinical Trial;

(b) information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Test Article that must be disclosed pursuant to law, rule or regulation for the purposes of protecting the public health; or

(c) information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, Freedom of Information Act (FOIA) request(s), or required to be disclosed by a court of competent jurisdiction or governmental authority.

"**Critical Event**" means any unanticipated study-related incident that is likely to cause or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity.

"**Data and Safety Monitoring Board**" **(DSMB)** is an independent group of experts that advises the NIAID and the Investigators. The primary responsibilities of the DSMB are to: (i) to periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (ii) to make recommendations to NIAID concerning the continuation, modification, or termination of the Clinical Trial.

"**Effective Date**" means the date of the last signature of the authorized representatives of the Parties executing this Agreement.

"**Electronic Common Technical Document**" **(eCTD)** means the standard format for electronic regulatory submissions as described in the most recent final revision to FDA Guidance for Industry entitled "Providing Regulatory Submissions in Electronic Format — Certain Human

Pharmaceutical Product Applications and Related Submissions Using the Electronic Common Technical Document Specifications."

"**Food and Drug Administration**" **(FDA)** means the U.S. Food and Drug Administration.

"**Government**" means the federal government of the United States of America.

"**Health Authority**" or "**HA**" means any non-U.S. Health Authority used when the Clinical Trial is being conducted in whole or in part at a non-U.S. Clinical Research Site requiring the use of non-U.S. regulatory agencies.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. Part 46, a living individual about whom an Investigator conducting research obtains:

(a) information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes the information or biospecimens; or

(b) obtains, uses, studies, analyzes, or generates Identifiable Private Information or identifiable biospecimens.

"**Identifiable Private Information**" (**IPI)** means private information about a Human Subject from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

"**Identifiable, Sensitive Information**" (**ISI**) means, in accordance with the definition of 42 U.S.C. 241(d)(4), information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or other research as described in 42 U.S.C. 241(d)(1)(A), and as applied by NIH Policy, where the following may occur:

- an individual is identified,
- IPI is included, or
- for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

"**Informed Consent Form**" (**ICF**) means a signed and documented form in which each Human Subject voluntarily consents or confirms his or her willingness to participate in a particular clinical trial after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. The informed consent form satisfies the requirements of ICH E6, 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**INSIGHT**" means the International Network for Strategic Initiatives in Global HIV Trials funded under combination of (1) a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI) and (2) an Award from NIAID to the University of Minnesota.

"**Institutional Review Board**" (**IRB)** or "**Independent Ethics Committee**" (**IEC**) means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects (Revised January 15, 2001)

and 21 C.F.R. Part 56, Subpart C: IRB Functions and Operations (as amended June 18, 1991), and other applicable regulations, an independent body comprising medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of the Human Subjects involved in a Clinical Trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use**" **(ICH)**. ICH refers to one or all of the following requirements used throughout this Agreement:

- **ICH E2F**: "Development Safety Update Report", including the latest finalized revision, if any.
- **ICH E3**: "Structure and Content of Clinical Study Reports", including the latest finalized revision, if any.
- **ICH E6**: "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance" for Industry, published in the Federal register (83 Federal Register 8882 (2018)), including the latest finalized revision. Also referred to as **"FDA Good Clinical Practice Guidelines**".
- **ICH Q7**: "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" published in the Federal register (66 Federal Register 49028-9 (2001)), including the latest finalized revision, if any.

"**Invention**" means any invention or discovery that is or may be patentable or otherwise protected under 35 U.S.C., or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act, 7 U.S.C. §§ 2321 *et seq*.

"**Investigational New Drug Application**" **(IND)** is filed in accordance with 21 C.F.R. Part 312 under which clinical investigation of a Test Article (an experimental drug or biologic) is performed in Human Subjects in the United States or intended to support a United States licensing action.

"**Investigator**" means, in accordance with 21 C.F.R. Part 312.3, an individual who actually conducts a clinical trial, that is, who directs the administration or dispensation of Test Article to a subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, "Investigator(s)" means the individual(s) identified as responsible for the conduct of the Clinical Trial at the Clinical Research Site.

"**Investigator Brochure**" **(IB)** means, in accordance with the definition in 21 C.F.R. Part 312.23(a)(5), a document containing information about the Test Article, including animal screening, preclinical toxicology, and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the Test Article or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Test Article.

"**Leidos Biomedical Research**" **(Leidos)** means the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory activities related to NIAID (DCR)'s clinical research. Leidos operates pursuant to a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI).

"Office of Human Research Protections" (OHRP) means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"Party" means an entity entering into this Agreement, referred to individually as the "Party" and collectively as the "Parties".

"**Patent**" means any issued United States patent, any international counterpart and any corresponding grant by a non-U.S. government in place of a patent.

"**PETAL**" means Prevention and Early Treatment of Acute Lung Injury, a clinical trials network funded by NHLBI in accordance with the terms of an Award.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV3b/INSIGHT015, "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with Acute Respiratory Distress Syndrome Associated with COVID-19 (TESICO)" and any company/product specific associated appendices incorporated therein. A Protocol describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. This Clinical Trial Agreement will be governed by the most recent version of the Protocol, and should this Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement in other matters, the terms of this Agreement will govern.

"**Protocol Team**" means the team, under the direction of NIAID, responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. The Protocol Team will include (b)(4)

(b)(4)

"**Regulatory Application**" or "RA" means an IND-equivalent, non-U.S. Regulatory Application, applicable when the Clinical Trial is being conducted in whole or in part at a non-U.S. clinical research site.

"Serious Adverse Event" means the definition as stated in the Protocol.

"**Serious Suspected Adverse Reaction**" means the definition stated in the Protocol.

"**Sponsor**" means, in accordance with the definition in 21 C.F.R. Part 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing Clinical Trials with Test Article, and is sometimes referred to as the "IND/RA holder". The Office of Clinical Research Policy and Regulatory Operations within the NIAID Division of Clinical Research is the IND/RA holder and sponsor of record for this Clinical Trial. Additionally, in accordance with 21 C.F.R. § 312.52(a) and any applicable HA requirements, several sponsor responsibilities will be transferred to the University of Minnesota Statistical and Data Management Center and to Leidos Biomedical Research.

"Statistical and Data Management Center" or **"SDMC"** means the management center at the University of Minnesota responsible for providing statistical and data management services for INSIGHT clinical trials, including the Clinical Trial that is the subject of this Agreement in accordance with the terms of a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI). The SDMC subcontracts with International Coordinating Centers (ICCs) that work with clinical sites in many different countries and with a drug distribution company that has drug depots in the United States and the United Kingdom. References to the "SDMC" in this Agreement refer to the University of Minnesota and the ICCs and drug distribution company, which is a University of Minnesota subcontractor.

"Suspected Adverse Reaction" means the definition as stated in the Protocol.

"**Test Article**" means, in accordance with 21 C.F.R. Part 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301, *et seq*., Pub. L.No.75-717, 52 Stat. 1040 (1938), as amended. In this Agreement, remdesivir and matching placebo are referred to as the "Test Article", individually and collectively.

"Unexpected Adverse Event" means the definition as stated in the Protocol.

"**Serious and Unexpected Suspected Adverse Reaction (SUSAR)**" means the definition stated in the Protocol.

"VA" means the U.S. Department of Veterans Affairs.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 The Company acknowledges that the NIAID and NHLBI fund the Clinical Research Sites under Awards and, therefore, the Clinical Research Sites may have certain existing legal obligations to the NIAID and NHLBI.

2.2 (b)(4)

2.3 The NIAID will use its best efforts to not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:

(i) Debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or

(ii) Suspended by the Office for Human Research Protections (OHRP) as a clinical research site under 45 C.F.R. Part 46, and

2.3.2 Any person convicted of a felony under federal law for conduct:

(i) Relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device,

New Drug Application (NDA), Biologics License Application (BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or

(ii) Otherwise relating to the regulation of any drug product or medical device under the FD&C Act.

2.3.3 Any person performing services in connection with this Clinical Trial that has been disqualified as a clinical investigator under 21 C.F.R. Part 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required under 21 C.F.R. Part 312.53.

2.4 If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party immediately.

2.5 The Awards require that Investigators, the Clinical Research Site, and other Clinical Trial personnel conduct the Clinical Trial in accordance with good clinical practice, including as defined by the ICH and comply with all applicable U.S. and foreign government, state and local laws, regulations and guidelines, including but not limited to those related to Human Subjects protection, Investigator qualifications, and Test Article where applicable.

2.6 The Parties agree that this Protocol will be conducted only at the Clinical Research Sites selected by NIAID (DCR), SDMC, and collaborating networks. However, the Company can conduct, at its own expense and under its own IND, additional clinical trials with the Test Article, including at the Clinical Research Site(s).

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND/RA.** The NIAID (DCR) will be responsible for the submission of an IND/RA covering the Protocol to the FDA/HA. The IND/RA will satisfy all of the requirements of the FDA/HA and as applicable, will comply with eCTD format requirements. Company agrees to provide all requested documents for IND submission to NIAID (DCR) in eCTD format. The Company will provide a letter granting the FDA/HA permission to cross-reference the Company's pertinent Drug Master File (DMF), New Drug Application (NDA), Biologics License Application (BLA), and/or INDs/RAs in support of any required NIAID (DCR) IND/RA for the Clinical Trial, and in return, the NIAID (DCR) will also provide a letter to the Company, if requested by the Company, granting the FDA/HA permission to cross-reference any required IND/RA filed by the NIAID (DCR) for this Clinical Trial. The NIAID (DCR) will promptly provide a copy of all IND/RA submissions (together with any and all ancillary documents) to the Company for the Clinical Trial at the time they are submitted to the FDA/HA. The confidential information of any third party will be removed.

3.2 NIAID (DCR) may delegate regulatory obligations to one or more third parties to facilitate NIAID's oversight, monitoring, and administration of the Clinical Trial at Clinical Research Sites outside of the United States. NIAID (DCR)'s third party delegate(s) will submit any clinical trial application and subsequent reports to all applicable HAs outside of the United States.

3.3 **Clinical Research Site Monitoring.** The NIAID (DCR), or its designee, will be responsible for Clinical Research Site monitoring and quality assurance of all data in accordance with the clinical monitoring plan for the Clinical Trial. Monitoring will be done in compliance with FDA Good Clinical Practice Guidelines (ICH) (E6). The NIAID will communicate any Critical Event findings from clinical monitors to the Company in a timely manner.

3.4 **Safety Reporting**

3.4.1 The NIAID (DCR) will collect Adverse Event reports according to the procedure outlined in the Protocol and in timeframes consistent with 21 C.F.R. § 312.32. The Clinical Research Sites will report Adverse Events to NIAID (DCR) in a timely manner and in accordance with the Protocol and Protocol Instruction Manual. NIAID (DCR) will assume responsibility for the regulatory reporting obligations for all individual and periodic safety reports to regulatory authorities, IRBs, ECs and investigators, including reporting of Adverse Events to the FDA/HA and will provide copies of all of the safety reports to Company manner. Such reports will be sent to:

Gilead Sciences, Inc.
Pharmacovigilance and Epidemiology
333 Lakeside Drive
Foster City, CA 94404
Fax: 650.522.5477
Tel: 650.522.5114
E-mail: Safety_FC@gilead.com

3.4.2 NIAID (DCR) will report all unexpected Serious Adverse Events ("SAEs") associated with the Test Article observed in this Clinical Trial to the FDA/HA and Company on a timely basis consistent with 21 C.F.R. § 312.32 and the Protocol. NIAID (DCR) will report other serious and non-serious adverse events to the FDA/HA and to Company on a timely basis consistent with 21 C.F.R. § 312.33 and the Protocol.

3.4.3 NIAID (DCR) will report all Serious Adverse Events ("SAEs") associated with the Test Article observed in this Clinical Trial to the Company at the Safety Reports Address listed in the Contacts section within fifteen (15) days of awareness.

3.4.4 (b)(4) (b)(4) Company shall contact the NIAID (DCR) Safety Office for information related to safety reports. NIAID will provide any additional information required to perform medical assessment of safety information provided to Company and provide reasonable assistance in providing any further information requested by Company.

3.4.5 Following completion of the Clinical Trial and upon reasonable request by the Company, NIAID (DCR) will provide to Gilead SAE data in the form of line listings to support reconciliation activities.

3.4.6 During the course of the study, if Company is requested by a regulatory agency to unblind an SAE or SUSAR report, the NIAID (DCR) will collaborate with Company to determine whether the report can be unblinded without undermining the scientific integrity of the Clinical Trial. NIAID (DCR) will provide the blinding information for study subjects randomized to the Test Article or the placebo to the Test Article to Company when all data forms have been keyed into the database for all subjects, data cleaning has been completed, and the Protocol Team has declared the study data set to be complete in a manner and format to be agreed between Company and NIAIDs that allows Company to unblind safety reports previously received from NIAIDs.

3.4.7 As the manufacturer of the Test Article, the Company will, in a timely manner consistent with FDA requirements and during the term of this Clinical Trial, provide the NIAID with any information regarding the safety and/or the toxicity of the Test Article that may impact Human Subject safety or Clinical Trial integrity as a safety letter communication. The NIAID will promptly transmit that information to all Investigators. All such reports or information to be submitted by the Company to the NIAID will be sent to:

NIAID Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
Email: rchspsafety@mail.nih.gov

3.5 (b)(4)

4. SAFETY MONITORING

Data Safety Monitoring Board (DSMB). A NIAID DSMB will monitor this Clinical Trial as described in the Protocol. NIAID will notify Company at least five (5) days in advance of any scheduled DSMB review. Company may participate in the open DSMB session and will be provided with open session reports and DSMB recommendations to NIAID (DCR). NIAID will promptly notify Gilead of any significant issues identified by the DSMB pertaining to the Company's Test Article and include Company in subsequent team meetings addressing DSMB concerns. NIAID will promptly provide recommendations derived from the DSMB to Company.

5. FDA MEETINGS/COMMUNICATIONS

5.1 If there are any discussions with the FDA/HA involving data obtained from this Clinical Trial, the NIAID (DCR), in consultation with the Company, will take the initiative in arranging meetings or conference calls with the FDA/HA. Formal meetings with the FDA/HA concerning the Clinical Trial design and/or data will be discussed and agreed upon in advance by the Company and the NIAID (DCR). The Company will have the right to participate in all formal meetings with the FDA/HA. The Company agrees not to contact the FDA/HA independent of the NIAID (DCR) concerning this Clinical Trial. (b)(4)

(b)(4)

(b)(4)

5.2 The Parties will promptly notify each other of:

5.2.1 any FDA/HA correspondence related to the Test Article or Protocol that is received by the Company or its Affiliates, or the NIAID;

5.2.2 any FDA/HA enforcement actions directed toward the Company or its Affiliates related to the Test Article, including but not limited to: warning letters, seizures, recalls, injunctions/consent decrees, rejection of regulatory submissions or withdrawal of approval for the Test Article;

5.2.3 any FDA/HA enforcement actions directed toward NIAID related to the conduct of the Clinical Trial;

5.2.4 any criminal investigations related to the conduct of the Clinical Trial;

5.2.5 any proceedings to debar the Company or its Affiliates, or the NIAID or individuals providing services for the Clinical Trial employed under a contract to the Company and/or its Affiliates, or to the NIAID.

5.3 The Company will also promptly notify NIAID (DCR) of any action taken by the FDA/HA regarding manufacturing of the Test Article that would impact the safety of Human Subjects in the Clinical Trial.

6. SUPPLY, DISTRIBUTION, AND USE OF TEST ARTICLE

6.1 **Supply**. (b)(4) (b)(4) in quantities and conditions sufficient to complete the Protocol and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Test Article. Company will be responsible solely for primary labeling containing product specific information for the Test Article used in the Clinical Trial.

6.2 **Distribution.**

6.2.1 The Company will ship the Test Article to central distribution drug depot(s) to be arranged by NIAID (DCR) and the SDMC as mutually agreed by the Parties. The Company will provide specific storage and/or shipping instructions for the Test Article to the NIAID (DCR), the SDMC, the central distribution drug depot(s), and/or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. The Company warrants that any packaging for hazardous material provided by the Company meets Department of Transportation regulatory requirements for use at the Clinical Research Site to include provision of Material Safety Data Sheets for the Test Article.

6.2.2 The Test Article must be received by the central distribution drug depot(s) in usable condition and accompanied by Material Safety Data Sheet (MSDS), specific storage and shipping instructions, stability and/or expiration dating information and the finally signed and dated Certificate of Analysis (COA) for each lot of Test Article sent. The Company will also provide documentation to support the cGMP status of the Test Article. If the Company performs ongoing stability testing for each lot of

Test Article sent, then the Company will also provide updated retest or expiration dates for those respective lots to NIAID (DCR) and the SDMC in a timely manner.

6.2.3 If there is evidence that the Test Article that arrived at the central distribution drug depot(s) has not been delivered according to the defined shipping instructions or there is evidence of damage to the Test Article container or container closure system, NIAID will ensure the SDMC contacts the Company to inform them of the condition of the received Test Article and to determine together with the Company whether the Test Article is usable or if it must be replaced. If the Test Article must be replaced, the Company will replace it at no cost to NIAID (DCR), the central distribution drug depot(s), or the Clinical Research Sites.

6.3 **Use.**

6.3.1 (b)(4)

6.3.2 The NIAID (DCR), pursuant to the Awards, will use best efforts to confirm that the Investigators:

(i) use the Test Article only in accordance with the Protocol and for no other purpose;
(ii) not transfer the Test Article to any parties except the Company; and
(iii) not chemically modify, replicate, make derivatives of, or reverse engineer the Test Article unless mutually agreed to in advance, in writing, by the Parties; and
(iv) comply with all applicable laws, rules and regulations.

6.4 **Disposition of Unused Test Article.** (b)(4)

(b)(4)

6.5 **Warranty.** The Company represents and warrants that the Test Article supplied at the time of shipment shall be manufactured and released according to the principles of current Good Manufacturing Practice, and when administered in accordance with Protocol, it is suitable and meets all required specifications for human use. EXCEPT FOR THE FOREGOING, COMPANY PROVIDES THE TEST ARTICLE "AS IS", WITH NO WARRANTY, EXPRESS OR IMPLIED OR STATUTORY, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY, TITLE, NON-INFRINGEMENT, EXCLUSIVITY OR FITNESS FOR A PARTICULAR PURPOSE.

6.6 **Post-Clinical Trial Plan**. The NIAID agrees, and will use best efforts to confirm that the Clinical Research Sites and Investigator agree, that Company shall not be responsible for providing any Test Article or any other products or therapy to Human Subjects following their respective completion of the Clinical Trial.

6.7 **Source.**

6.7.1 In the event the Company elects to terminate its development of Test Article for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to the NIAID (DCR) within ninety (90) calendar days of discontinuation, then the Company will provide the NIAID (DCR) with sufficient quantity of Test Article and other resources necessary to complete the Protocol.

6.7.2 The Parties also agree that should this Agreement be terminated prior to completion of the Protocol, the Protocol will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol and Company will supply enough Test Article to complete the Protocol in accordance with this Agreement.

7. INVESTIGATOR'S BROCHURE

Company will provide a current IB in eCTD format for all applicable components of the Test Article, and any later revisions and addenda to the IB for the Test Article, including a summary of changes (SOC), to NIAID (DCR), as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Section 13 (Confidential Information) of this Agreement. Company agrees to provide NIAID (DCR) any updated version of the IB, with the SOC, within fifteen (15) days of issuance. Company will send the IB and SOC to the NIAID (DCR) to the attention of the NIAID contact for regulatory matters identified in Article 26. NIAID (DCR), through the SDMC, will distribute the IB to the Clinical Research Sites. NIAID (DCR) will address requests for IBs, including updated versions and SOCs, to:

(b)(6)
Senior Director, Clinical Research
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404Phone: (b)(6)
E-mail: (b)(6) @gilead.com

8. PROTOCOL DEVELOPMENT AND REGISTRATION

8.1 Development and management of the Protocol, evaluation of data/results, proposal of amendments and recommendations for early termination shall be the responsibility of the Protocol Team.

8.2 The Parties agree that enrollment in the Clinical Trial will not start until the version of the Protocol to be used has been reviewed in advance by the Protocol Team; approved (stipulations met/resolved) by the relevant IRB(s)/IEC(s) and the NIAID (DCR) in writing; and submitted to the FDA/HA under an existing IND/RA, any FDA/HA wait period has been satisfied, any FDA/HA clinical hold issues have been responded to satisfactorily, and notification has been received by NIAID (DCR) from the FDA/HA that the Clinical Trial in the IND/RA may begin.

8.3 (b)(4)

(b)(4)

8.4 The NIAID (DCR), through its contractors or designees on behalf of NIAID, will be responsible for performing the randomization.

8.5 All NIAID (DCR)-sponsored network protocols which include the informed consent must meet all federal mandates as well as NIAID (DCR) requirements to ensure the welfare of Human Subjects in the Clinical Trial. Each Clinical Research Site, prior to participating in any NIAID (DCR)-sponsored study, must submit its informed consent to the NIAID (DCR) or designee for review.

9. CASE REPORT FORM DEVELOPMENT AND STATISTICAL ANALYSIS PLAN DEVELOPMENT

The NIAID (DCR), through the SDMC, will be responsible for the development and subsequent revisions, if any, of the Case Report Forms and the statistical analysis plan for the Clinical Trial with appropriate review and comment by the Protocol Team prior to implementation.

10. HUMAN SUBJECTS PROTECTION

10.1 The NIAID and the Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The Informed Consent Form of each Human Subject participating in the Clinical Trial at a Clinical Research Site(s) will be obtained prospectively using an IRB/IEC approved informed consent process that complies with all applicable laws and regulations. (b)(4)

(b)(4)

10.2 The NIAID and the Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46, Protection of Human Subjects (as currently revised), and in a Certificate of Confidentiality issued by NIH in accordance with 42 U.S.C 241(d) of the Public Health Service Act.

Therefore:

10.2.1 Any ISI that Company receives from NIH is covered by a CoC and therefore all copies of ISI are immune from the legal process, and will not, without the consent of the Human Subject, be admissible as evidence or used for any purpose in any action, suit, or other judicial, legislative, or administrative proceeding.

10.2.2 The NIAID and the Company will maintain the confidentiality of ISI of Human Subjects collected under the Clinical Trial and protect the privacy of each of the individual Human Subjects in the Clinical Trial unless disclosure is required by law (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding. Prior to making any

permitted disclosures, Company will ensure that any recipient of ISI protected by a CoC is aware of its confidential nature and the requirement to comply with the CoC.

10.2.3 The NIAID and the Company agree that neither Party will, nor will they allow their respective employees and contractors or any entity or person working on their behalf to, include ISI that could lead to identification of individual Human Subjects in any release of data, reports or publications related to the Clinical Trial. The NIAID will use best efforts to confirm that the Clinical Research Site and Investigators do not include ISI that could lead to identification of individual Human Subjects in any release of data, reports or publications related to the Clinical Trial.

10.2.4 The NIAID and the Company agree that neither Party will, nor will they allow their respective employees and contractors or any entity or person working on their behalf to, use ISI about Human Subjects for any purpose not stated in the Protocol without the consent of the Human Subject, the other Party, and local site IRB approval, unless such purpose is required or allowed by law. The NIAID will use best efforts to confirm that the Clinical Research Site and Investigators do not use ISI for any purpose not stated in the Protocol and Informed Consent Form without the written consent of the Human Subject, both Parties, and appropriate IRB approval, unless such purpose is required or allowed by law.

10.2.5 The NIAID and the Company agree to comply with the determinations of all IRBs overseeing the Clinical Trial. If a Party does not agree with a determination, the Parties will negotiate a mutually agreeable resolution.

10.2.6 Specimens and related data provided to the Company during and after the Clinical Trial will be encoded in accordance with applicable U.S., foreign government, state and local laws, regulations and guidelines. Unequivocally, neither IPI nor the key linking coded data to individuals will be released to the Company.

11. DATA ANALYSIS AND MANAGEMENT

11.1 Each Clinical Research Site will be responsible for gathering the data obtained from the Clinical Trial at an Investigator's Clinical Research Site, and submitting that data to the SDMC. The Protocol Team, which includes Company representatives, will be responsible for the scientific reporting of the data.

11.2 The NIAID (DCR), through the SDMC, will have responsibility for all Clinical Trial data management, including but not limited to: collection, entry, and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

11.3 All data obtained from the Clinical Trial will be in the custody of the Investigator or the Clinical Research Site, as applicable, which produces such data. However, (b)(4); (b)(3):35 U.S.C. § 209(a)

(b)(4); (b)(3):35 U.S.C. § 209(a)

11.4 Promptly upon completion of the data analyses related to the Test Article, the NIAID will require the SDMC to transfer to the Company a copy of the complete data analysis set related to the Test Article. (b)(4); (b)(3):35 U.S.C. § 209(a)

(b)(4); (b)(3):35 U.S.C. § 209(a)

11.5 (b)(4); (b)(3):35 U.S.C. § 209(a)

11.6 Subject to the right of the NIAID (DCR) and the Investigators to publish the data from this Clinical Trial as set forth in the Publications and Press Releases Section of this Agreement,

(b)(4); (b)(3):35 U.S.C. § 209(a)

The NIAID (DCR) and/or the Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA/HA, and the Securities and Exchange Commission (SEC) for all legitimate public health, regulatory or business purposes. The foregoing notwithstanding, except for information related to regulatory or safety issues or under emergency circumstances where it is not practicable to do so and to the extent permitted by law, the NIAID (DCR) will not release information regarding the Clinical Trial to governmental organizations without prior written notification of the information and a copy thereof to the Company.

11.7 Given the nature of the SARS-CoV-2 pandemic, it is anticipated that novel genetic variants of the SARS-CoV-2 will evolve which may impact the potency and/or efficacy of the Test Article. The Parties agree, in a separate agreement under mutually agreeable terms, to cooperate in good faith in the sharing of data that relates to the potency of the Test Article against variants that arise that have the potential to impact the efficacy of the Test Article at any of the global Clinical Research Sites.

12. PUBLICATIONS AND PRESS RELEASES

12.1 Except as specifically set forth in Section 12.3, any publications based on the results of the Clinical Trial and originating from NIAID (DCR), Investigators or the Clinical Research Site will conform to the applicable publication policy for the Clinical Trial. Unless requested otherwise by the Company, the NIAID (DCR) will acknowledge the Company as the source of the Test Article in any NIAID (DCR) publication resulting from the Clinical Trial and will use best efforts to confirm that the Investigators and the Clinical Research Site do the same in their publications resulting from the Clinical Trial.

12.2 Recognizing that employees of either Party may play an important role in the design, analysis, and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the generally accepted customs pertaining to authorship, and NIAID (DCR) will use best efforts to confirm that the Investigators and the Clinical Research Site(s) include appropriate individuals from both Parties in the authorship of their publications resulting from the Clinical Trial.

Notwithstanding anything to the contrary in the applicable publication policies or elsewhere, each Party will provide, and the NIAID will use best efforts to confirm that the Investigators and the Clinical Research Site(s) will provide, the other Party with a copy of any abstract, oral presentation material, or manuscript prior to submission for publication or presentation, as applicable, with sufficient time [Abstracts and oral presentation materials: five (5) business days; Manuscripts: ten (10) business days] for review and comment. Each Party agrees that, following the receiving Party's review of the abstract, oral presentation material and/or manuscript for the maximum periods of time specified above, if no comment is received by the submitting Party, the submitting Party will be free to publish, present or use any Clinical Trial data. The receiving Party will maintain the proposed publication or public disclosure of the submitting Party as Confidential Information until publication or public disclosure by the submitting Party. Notwithstanding the timelines described above, the Parties agree that expedient publication of the Clinical Trial results is necessary for the public good and the Parties agree to work in good faith to allow expeditious publication of the Clinical Trial results.

12.3 All publications or other disclosures may be delayed for up to (b)(4) (b)(4) for publications and (b)(4) for abstracts upon written request by either Party as necessary to preserve U.S. or foreign patent or other intellectual property rights. Additionally, if requested by the Company during the review period defined in Section 12.2, NIAID (DCR) will, and will use best efforts to confirm that the Investigators and the Clinical Research Site will, delete from any publication or presentation any information claimed by the Company to be Company's Confidential Information. If the Company requests redaction of its Confidential Information, the Company will make reasonable efforts to supply substitute non-confidential information when practicable in order to allow the publication to go forward.

12.4 Each Party will provide, and NIAID will use best efforts to confirm that Investigators and the Clinical Research Site will provide, a copy of any proposed press release to the other Party for review and comment at least (b)(4) in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, if no comment is received by the submitting Party and/or the Investigators or Clinical Research Sites, the submitting Party, Investigators, or Clinical Research Sites will be free to publish the press release.

13. CONFIDENTIAL INFORMATION

13.1 Either Party may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct the Clinical Trial. The disclosing Party will endeavor to place a confidentiality notice on all the

Confidential Information. The disclosing Party will endeavor to reduce confidential non-written communications to writing within thirty (30) business days of first disclosure. Each Party receiving Confidential Information agrees that any information so designated will be maintained as Confidential Information in accordance with this Agreement and used by it only for the purposes of the Clinical Trial. Any Party may object to the designation of information as Confidential by the other Party. If such an objection is raised, the Parties agree to discuss and resolve that objection in good faith.

13.2 Unless expressly provided otherwise, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA), 5 U.S.C. § 552, 45 C.F.R. Part 5, or other applicable laws and/or regulations to disclose the Confidential Information, except that the NIAID may disclose the Company's Confidential Information to Government contractors and associates, and the Investigators, their respective IRBs/IECs, and other parties to the degree required for the conduct of the Clinical Trial. The NIAID will use best efforts to confirm that the Investigators and the Clinical Research Site(s) receiving the Company's Confidential Information maintain the confidentiality of Confidential Information consistent with the terms of this Agreement.

13.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. While the NIAID will endeavor to control the distribution of the Protocol document itself, the Company acknowledges that some Government documents are available (with abstracts) to the public under the Freedom of Information Act. In addition, NIAID policy requires posting of information and certain documents, including the Protocol and statistical analysis plan (SAP) be posted on the ClinicalTrials.gov registry of clinical studies, available through the NIH Website, consistent with the Food and Drug Administration Amendments Act of 2007, 121 STAT. 823. The NIAID shall be responsible for submitting all Clinical Trial information to Clinical Trails.gov.

13.4 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given a reasonable opportunity to seek a court order to enjoin from disclosure.

13.5 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above or five (5) years after the expiration or termination date of this Agreement. Either Party may request an extension to this term when necessary to protect Confidential Information relating to the Test Article. This term does NOT apply to ISI, for which the obligation to maintain confidentiality will extend indefinitely.

14. INTELLECTUAL PROPERTY

14.1 Ownership of any Invention conceived or first actually reduced to practice solely or jointly by NIAID employees, the Clinical Research Site and Investigators, or other NIAID contractors or grantees as a consequence of conducting the Clinical Trial and involving the

Test Article, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party acquires by virtue of this Agreement any right, title, nor interest in or to any issued Patents or pending patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by the Company to the NIAID (DCR), other than the limited right to use the Test Article for the performance of the Protocol in accordance with the terms of this Agreement.

14.2 **NIAID Intellectual Property.**

14.2.1 The Government will retain title to any Patent, pending patent applications or other intellectual property rights in Inventions conceived or first actually reduced to practice solely by NIAID employees in the course of the Clinical Trial.

14.2.2 The NIAID agrees to notify the Company of any NIAID sole or joint Invention and to disclose it to the Company under an appropriate confidentiality agreement. The Company may apply for nonexclusive or exclusive license rights to any such patentable Invention made by NIAID employees that might arise during the Clinical Trial and the NIH will consider the Company's application for a nonexclusive or exclusive license consistent with 37 C.F.R. Part 404.

14.3 **Company Intellectual Property**. The Company will retain title to any Patents, pending patent applications, or other intellectual property rights in Inventions conceived by its employees during the course of the Clinical Trial.

14.4 **Clinical Research Site/Investigator Intellectual Property.**

This Agreement does not grant any license or obligation to license any intellectual property of the Clinical Research Sites or preclude the creation of intellectual property rights, including but not limited to Inventions conceived by the Investigators or other Government contractors or grantees during the course of the clinical research. The Company may enter into a separate agreement with the Clinical Research Site or Investigators, regarding intellectual property rights and confidentiality that do not interfere with the conduct of this Clinical Trial, contradict the terms of this Agreement or contradict the terms of the relevant Award.

14.5 **Joint NIAID-Company Intellectual Property.** The NIAID and the Company will have joint intellectual property rights in Inventions conceived or first actually reduced to practice jointly by their employees during the course of the clinical research. Company may apply for a non-exclusive or exclusive license to the NIAID rights in such Inventions in accordance with the 37 CFR 404.

14.6 The NIAID represents and certifies that any intellectual property rights granted to any third party supplier for the Clinical Trial will not be greater than the intellectual property rights provided to the Company under this Agreement, and in all cases consistent and compliant with 37 CFR 404 and other applicable regulations and policies.

15. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

16. LIABILITY, INDEMNIFICATION, INSURANCE

16.1 **Liability.** Each Party shall be liable for any loss, claim, damage or liability that it incurs as a result of its direct activities under this Agreement, except that NIAID (DCR), as an agency of the U.S. Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171.

16.2 **Indemnification.** NIAID is prohibited under the Anti-Deficiency Act, 31 U.S.C. § 1341 from indemnifying Company for any losses incurred as a result of this Clinical Trial. Each Party will be liable for the losses, claims, damages or liabilities that it incurs as a result of its activities under this Agreement. Company's right and obligation to defend NIAID and Company's control over the defense and settlement of any claim against NIAID will be subject to the consent of NIAID and the Department of Justice.

The Company will defend, indemnify and hold harmless NIAID, NHLBI, and the VA, and their grantees and contractors and their respective agents and employees associated with the Clinical Trial ("**Indemnitee(s)**") from any and all liabilities, damages, losses, claims, action, suits and expenses brought by a third party (excluding the cost of the time and effort of Indemnitees' own employees), including reasonable attorneys' fees and court costs (collectively "**Claims**") to the extent arising from injury or death to Human Subjects in the Clinical Trial for adverse drug experiences to Human Subjects to the extent caused in whole or in part by the manufacture, labeling, or packaging of the Test Article prior to shipment to the Clinical Research Site; provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if all of the following conditions are met:

16.2.1 The Claim was not proximately caused by the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, this Agreement, the agreements between the Clinical Research Site, Investigators, or other NIAID employees, contractors or grantees, all applicable laws, rules and regulations, and/or any written instructions from the Company;

16.2.2 The Claim was not caused by the negligence, recklessness or willful misconduct of any Indemnitee, provided that any action properly taken by the Indemnitee in compliance with written instructions from the Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if the injury or death giving rise to a Claim is jointly caused by the negligence of any Indemnitee and the administration or use of the Test Article in accordance with the Protocol, then Company will provide defense and indemnification only to the extent such injury or death was caused by the manufacture, labeling or packaging prior to shipment to the Clinical Research Site of the Test Article.

16.2.3 Company is promptly notified of the Claim, provided that the failure to give such notice will not abrogate or diminish Company's defense and indemnity obligation if Company has or receives knowledge of the existence of the Claim by any other means or if such failure does not prejudice Company's ability to defend the Claim.

16.2.4 Company will have sole control over the defense and settlement of the Claim(s) directed against Company.

16.2.5 Company will have the right to select defense counsel and to direct the defense and settlement of the Claim(s) directed against Company.

16.2.6 Company will provide a diligent defense against and/or settlement of any Claims for which defense and indemnification are provided under this Agreement whether such Claims are rightfully or wrongfully made. Company will have the right to settle such Claims, at Company's sole expense and in Company's sole discretion. Indemnitee(s) will fully cooperate, at Company's expense, with Company and its legal representatives in the investigation and defense of any Claim for which defense and indemnification are provided under this Agreement.

16.2.7 The Indemnitee(s) will at all times have the right to fully participate in the defense of any Claim at their own expense and for their own account. If Company will, within a reasonable time after notice, fail to defend any Claim for which defense and indemnification are provided under this Agreement, the Indemnitee(s) will have the right, but not the obligation, to undertake the defense of and to compromise or settle the Claim on behalf, for the account, and at the risk of Company.

16.3 **Insurance**. The Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the Company's indemnification obligations described above. Upon request, the Company will provide evidence of its insurance or self-insurance to NIAID (DCR).

17. DISPUTES

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute through good faith negotiations within thirty (30) calendar days after notification thereof, the dispute will be referred to the Director of DCR, NIAID (or his/her designee) and an appropriate authorized representative of the Company for resolution. If the Director of DCR, NIAID (or his/her designee) and the authorized representative of the Company are unable to jointly resolve the dispute through good faith negotiations within thirty (30) calendar days, the dispute will be referred to the Director of NIAID (or his/her designee) and the authorized representative of Company. If the Director of NIAID (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute through good faith negotiations within fifteen (15) calendar days, either Party may pursue any and all administrative or judicial remedies that may be available.

18. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the other Party, enter into any contract, warranty, or representation as to any matter. Neither Party will be bound by the acts of the other Party.

19. NON-ENDORSEMENT

By entering into this Agreement, the NIAID does not directly or indirectly endorse any product or service provided, or to be provided, by the Company. The Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However, the Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

20. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

21. SURVIVABILITY

The provisions of Sections 1 (Definitions), 2 (Clinical Research Site and Investigators), 3 (Investigational New Drug Application Sponsorship), 4 (Safety Monitoring), 5 (FDA Meetings/Communications), 6 (Supply, Distribution, and Use of Test Article), 8 (Protocol Development and Registration), 10 (Human Subjects Protection), 11 (Data Analysis and Management), 12 (Publications and Press Releases), 13 (Confidential Information), 14 (Intellectual Property), 15 (Force Majeure), 16 (Liability, Indemnification, Insurance), 17 (Disputes), 18 (Independent Contractors), 19 (Non-Endorsement), 20 (Amendments), this Section 21 (Survivability), 22 (Entire Agreement and Severability), 23 (Assignment), 24 (Applicable Law), 25 (Term and Termination), 26 (Notices) and 27 (Counterparts) will survive the expiration or earlier termination of this Agreement.

22. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement, provided that the confidentiality obligations contained in any prior agreement between the Parties and any confidentiality agreement entered into between the Parties shall continue in full force and effect in accordance with its terms. The provisions of this Agreement are severable and, in the event that any provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

23. ASSIGNMENT

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without the prior written consent of the other Party, except that the Company may assign this Agreement, with advance notice to NIAID, to its affiliates or a

successor-in-interest to its business through merger or consolidation, to which this Agreement pertains, provided that such successor assumes all obligations of the Company herein.

24. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

25. TERM AND TERMINATION

25.1 Unless terminated sooner in accordance with this Section 25, this Agreement will expire upon completion of all Clinical Trial activities and delivery of data analysis related to the Protocol, and return of unused Test Article to the Company.

25.2 The Parties may terminate this Agreement at any time by mutual written consent.

25.3 Either Party may unilaterally terminate this Agreement at any time by giving written notice at least thirty (30) calendar days prior to the desired termination date.

25.4 The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically appropriate. In that event, each enrolled Human Subject will be followed through the period outlined in the Protocol and the Company will supply enough Test Article to complete the Clinical Trial, without charge and on a schedule mutually agreed upon by the Parties to ensure the agreed upon supply of unexpired Test Article.

25.5 In the event the Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution, the Company must notify NIAID within at least thirty (30) calendar days of the dissolution.

26. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt), or via facsimile, Portable Document Format (PDF), or email followed by conformational hard copies sent via courier when it is necessary to receive or deliver documents within a very short period of time [less than one (1) day].

For the Company:

For legal matters:
Gilead Sciences, Inc.
Attn: Corporate Legal Affairs
333 Lakeside Drive
Foster City, CA 94404
Fax: (b)(4)
E-mail: (b)(4)

For regulatory matters:
(b)(6) (b)(6)
Tel: (b)(6)
E-mail: (b)(4)@gilead.com

For technical matters:
(b)(6)
Tel: (b)(6)
E-mail: (b)(6) @gilead.com

For NIAID (DCR):
H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
5601 Fishers Lane, Suite 6D
Rockville, MD 20892-9804
Phone: (b)(6)
Email: (b)(6) @niaid.nih.gov

For regulatory matters:
John Tierney, B.S.N., M.P.M
Clinical Research Oversight Manager
Office of Clinical Research Policy and Regulatory Operations
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9820
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

For clinical matters:
Elizabeth Higgs, M.D.
Global Health Science Advisor
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9802
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

27. COUNTERPARTS

This Agreement may be executed in counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. Signatures to this Agreement transmitted by fax, by electronic mail in portable document (.pdf) format, or by any other electronic means intended to preserve the original graphic and pictorial appearance of the Agreement, will have the same effect as physical delivery of the paper document bearing the original signature.

SIGNATURES BEGIN ON THE NEXT PAGE

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

FOR NIAID:

H. Clifford Lane

March 22, 2021

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

Date

FOR COMPANY:

(b)(6)

(b)(6)

(b)(6)

3/26/2021

Date

Clinical Research
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

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IND SPONSOR: NIAID

CLINICAL TRIAL AGREEMENT

For Clinical Trials Conducted at the National Institutes of Health

BETWEEN

THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

AND

GILEAD SCIENCES, INC.

DMID Protocol # 20-0013

Gilead No. CO-US-540-5947

A Multicenter Platform Trial of Putative Therapeutics for the Treatment of COVID-19 in Hospitalized Adults

[Short Title: Big Effect Trial (BET)]

Version 1.0 (August 11, 2020)

The National Institute of Allergy and Infectious Diseases ("**NIAID**"), an institute of the National Institutes of Health (NIH), which is part of the United States Government Department of Health and Human Services (HHS), as represented by the Division of Microbiology and Infectious Diseases (DMID) and Gilead Sciences, Inc. (together with its affiliates and subsidiaries, the "**Company**"), located at 333 Lakeside Drive, Foster City, California 94404 (individually referred to as the "**Party**" and collectively referred to as the "**Parties**") have agreed to cooperate in the conduct of a clinical trial at NIAID research sites, designated as DMID Protocol No. 20-0013, titled " A Multicenter Platform Trial of Putative Therapeutics for the Treatment of COVID-19 in Hospitalized Adults [Short Title: Big Effect Trial (BET)]." Based on the scientific and medical merit of this trial, the Company agrees to provide research support for the trial in an amount of Company's investigational compound remdesivir sufficient to complete the Protocol (b)(4); (b)(3):35 U.S.C. § 209(a) (b)(4); (b)(3):35 U.S.C. § 209(a) (b)(4); (b)(3):35 U.S.C. § 209(a) If NIAID subsequently requests any amounts in excess of those agreed-upon estimates, then, to the extent justified by the then current need for remdesivir under such appendix of the Protocol (b)(4); (b)(3):35 U.S.C. § 209(a) (b)(4); (b)(3):35 U.S.C. § 209(a) Gilead shall (b)(4); (b)(3):35 U.S.C. § 209(a) (b)(4); (b)(3):35 U.S.C. § 209(a) The Parties will mutually agree on the supply of any additional amounts of remdesivir under this Agreement.

This Agreement sets forth the terms and conditions under which this clinical trial, with the aforementioned titled protocol (the "Protocol"), will be managed and for Company access to data/results from this Protocol as necessary to achieve trial objectives.

The Company and the NIAID agree as follows:

1. DEFINITIONS

The terms listed in this Section have the meanings indicated throughout this Agreement. To the extent a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code (U.S.C.) or the Code of Federal Regulations (C.F.R.), the definition in the U.S.C. or C.F.R. will control.

"**Adverse Event**" (**AE)** means any untoward medical occurrence in a Human Subject to whom the Test Article has been administered. An adverse event does not necessarily have a causal relationship with the Test Article, that is, it can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Test Article, whether or not it is related to it. Adverse Event is further defined in ICH E6 Section 1.2 and 21 CFR 312.32.

"**Affiliates**" With respect to the Company, "Affiliates" means,

(i) any legal entity of which the securities or other ownership interests representing fifty per cent (50%) or more of the equity or fifty per cent (50%) or more of the ordinary voting power or fifty per cent (50%) or more of the general partnership interest are, at the time such determination is being made, owned, controlled or held, directly or indirectly, by such legal entity, or

(ii) any legal entity which, at the time such determination is being made, is controlling or under common control with, such legal entity.

As used (b)(4) the term "control", whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract or otherwise.

"**Agreement**" means this Clinical Trial Agreement or "CTA", all executed amendments and supplements to this Agreement and all schedules to this Agreement.

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"**Award**" means any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between NIAID and the awardee, who may subcontract or otherwise coordinate with the Clinical Research Sites.

"**Case Report Form**" **(CRF)** means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Certificate of Confidentiality**" (**CoC**) means a certificate issued by NIH pursuant to Section 301(d) of the Public Health Service Act (42 U.S.C. 241(d)), that protects the privacy of Human Subjects enrolled in the Protocol. With limited exceptions defined in 42 U.S.C. 241(d), the CoC protects from disclosure names or any information, documents or biospecimens containing ISI collected under the Protocol. Any investigator or institution not funded by NIH who receives a copy of ISI protected by a CoC issued by NIH, understand they are also subject to the requirements of subsection 301(d) of the Public Health Service Act and for ensuring that collaborators that are carrying out part of the research involving a copy of ISI protected by a CoC issued by NIH understand they are also subject to subsection 301(d) of the Public Health Service Act.

"**Clinical Research Site(s)**" means the site(s) that have agreements or Awards with NIAID where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Study Report**" in accordance with ICH E6 Section 1.13, is a written description of a Clinical Trial in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report. The Clinical Study Report contains information on results including reactogenicity, adverse events, immunogenicity and other clinical or laboratory observations made with respect to the intervention employed in conducting the Clinical Trial. A detailed description of the contents of a Clinical Study Report is found in ICH E3 "Structure and Content of Clinical Study Reports."

"**Clinical Trial**" is defined by the NIH as a research study[1] in which one or more human subjects[2] are prospectively assigned[3] to one or more interventions[4] (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.[5] In this Agreement, Clinical Trial means the Clinical Trial for the Protocol. ([1]See Common Rule definition of *research* at 45 CFR 46. [2]See Common Rule definition of *human subject* at 45 CFR 46. [3]The term "*prospectively assigned"* refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial. [4]An *intervention* is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. [5]*Health-related biomedical or behavioral outcome* is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life.) (See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html for more information.)

"**Completion of the Clinical Trial**" the Clinical Trial is complete when all data analyses under the Protocol have been performed.

"**Confidential Information**" means confidential scientific, proprietary, business, or financial information provided by one Party to the other Party (including, without limitation, any applicable Investigator's Brochure, clinical, preclinical or formulation data). For clarification, Confidential Information does not include:

(a) information that is within the public domain prior to the time of the disclosure by the disclosing Party to the receiving Party or thereafter becomes within the public domain other than as a result of disclosure by the receiving Party or any of its representatives in violation of this Agreement;

(b) information that was, on or before the date of disclosure in the possession of the receiving Party, as demonstrated by the receiving Party's independent records;

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(c) information that is acquired by the receiving Party from a third party not under an obligation of confidentiality;

(d) information that is hereafter independently developed by the receiving Party, without reference to or use of the Confidential Information received from the disclosing Party, as shown by the receiving Party's written records; or

(e) information that the disclosing Party expressly authorizes, in advance and in writing, the receiving Party to disclose.

Notwithstanding the foregoing, Confidential Information of a Party may be disclosed by the other Party to those persons and to the extent reasonably required by:

(a) information that is reasonably required by scientific standards for publication of the results of the Clinical Trial (including Clinical Trial methods and/or data) or any information that is necessary for other researchers to verify the results of the Clinical Trial;

(b) information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Test Article that must be disclosed pursuant to law, rule or regulation for the purposes of protecting the public health; or

(c) information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, Freedom of Information Act (FOIA) request(s), or required to be disclosed by a court of competent jurisdiction or governmental authority.

"**Data and Safety Monitoring Board**" **(DSMB)** is an independent group of experts that advises the NIAID and the Investigators. The primary responsibilities of the DSMB are to: (i) to periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (ii) to make recommendations to NIAID concerning the continuation, modification, or termination of the Clinical Trial.

"**Data Coordination Center**" **(DCC)** means an organization funded by the NIAID that receives, reviews, and performs data management tasks on the individual Human Subject Case Report Forms completed for this Clinical Trial. The Data Coordination Center for this Clinical Trial is Social & Scientific Systems, Inc.

"**Distributor**" means the NIAID contractor who may be distributing the Test Article to the Clinical Research Sites. The NIAID Distributor for this Clinical Trial is Fisher BioServices, Inc.

"**Effective Date**" means the date of the last signature of the authorized representatives of the Parties executing this Agreement.

"**Electronic Common Technical Document**" **(eCTD)** means the standard format for electronic regulatory submissions as described in the most recent final revision to FDA Guidance for Industry entitled "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the Electronic Common Technical Document Specifications."

"**Food and Drug Administration**" **(FDA)** means the U.S. Food and Drug Administration.

"**Government**" means the federal government of the United States of America.

"**Genome-Wide Association Study**" **(GWAS)** means any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. Part 46, a living individual about whom an Investigator conducting research obtains:

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(a) information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes the information or biospecimens; or

(b) obtains, uses, studies, analyzes, or generates Identifiable Private Information or identifiable biospecimens.

"**Identifiable Private Information**" (**IPI)** means private information about a Human Subject from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

"**Identifiable, Sensitive Information**" (**ISI**) means, in accordance with the definition of 42 U.S.C. 241(d)(4), information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or other research as described in 42 U.S.C. 241(d)(1)(A), and as applied by NIH Policy, where the following may occur:

- an individual is identified,
- IPI is included, or
- for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

"**Informed Consent Form**" (**ICF**) means a signed and documented form in which each Human Subject voluntarily consents or confirms his or her willingness to participate in a particular clinical trial after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. The informed consent form satisfies the requirements of ICH E6, 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**Institutional Review Board**" (**IRB)** means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects and 21 C.F.R. Part 56, and other applicable regulations, an independent body comprising medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of the Human Subjects involved in a Clinical Trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use**" **(ICH)**. ICH refers to one or all of the following requirements used throughout this Agreement:

(a) **ICH E2F**: "Development Safety Update Report", including the latest finalized revision, if any.

(b) **ICH E3**: "Structure and Content of Clinical Study Reports", including the latest finalized revision, if any.

(c) **ICH E6**: "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance" for Industry, published in the Federal register (83 Federal Register 8882 (2018)), including the latest finalized revision. Also referred to as **"FDA Good Clinical Practice Guidelines**".

(d) **ICH Q7**: "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" published in the Federal register (66 Federal Register 49028-9 (2001)), including the latest finalized revision, if any.

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"**Invention**" means any invention or discovery that is or may be patentable or otherwise protected under 35 U.S.C., or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act, 7 U.S.C. §§ 2321 *et seq*.

"**Investigational New Drug Application**" **(IND)** is filed in accordance with 21 C.F.R. Part 312 under which clinical investigation of a Test Article (an experimental drug or biologic) is performed in Human Subjects in the United States or intended to support a United States licensing action.

"**Investigator**" means, in accordance with 21 C.F.R. Part 312.3, an individual who actually conducts a clinical trial, that is, who directs the administration or dispensation of Test Article to a subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, "Investigator(s)" means the individual(s) identified as responsible for the conduct of the Clinical Trial at the Clinical Research Site.

"**Investigator Brochure**" **(IB)** means, in accordance with the definition in 21 C.F.R. Part 312.23(a)(5), a document containing information about the Test Article, including animal screening, preclinical toxicology, and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the Test Article or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Test Article.

"Office of Human Research Protections" (OHRP) means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"Party" means an entity entering into this Agreement, referred to individually as the "Party" and collectively as the "Parties".

"**Patent**" means any issued United States patent, any international counterpart and any corresponding grant by a non-U.S. government in place of a patent.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in DMID Protocol #20-0013 titled "A Multicenter Platform Trial of Putative Therapeutics for the Treatment of COVID-19 in Hospitalized Adults [Short Title: Big Effect Trial (BET)]". A Protocol describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. This Clinical Trial Agreement will be governed by the most recent version of the Protocol, and should this Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement in other matters, the terms of this Agreement will govern.

"**Protocol Team**" means the team, under the direction of NIAID, responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. (b)(4)

(b)(4)

Participation on the Protocol Team will be as agreed by the Parties and will take into account any special requirements of the Protocol design.

"**Serious Adverse Event**" or "**Serious Suspected Adverse Reaction**" means an adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical

events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

"**Sponsor**" means, in accordance with the definition in 21 C.F.R. Part 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing Clinical Trials with Test Article, and is sometimes referred to as the "IND holder". The Sponsor for the IND filing of the Protocol and the Clinical Trial is NIAID.

"**Suspected Adverse Reaction**" means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected Adverse Reaction is further defined in 21 CFR 312.32.

"**Test Article**" means, in accordance with 21 C.F.R. Part 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301, *et seq*., Pub. L.No.75-717, 52 Stat. 1040 (1938), as amended. In this Agreement, remdesivir and matching placebo are referred to as the "Test Article", individually and collectively.

"**Unexpected Adverse Event**" or "**Unexpected Suspected Adverse Reaction***"* means an adverse event or suspected adverse reaction which is considered "unexpected" because it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, when an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. Unexpected Adverse Event and Unexpected Suspected Adverse Reaction are further defined in 21 CFR 312.32.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 The Company acknowledges that the NIAID partners with the Clinical Research Sites and is the IND Sponsor for the Protocol and, therefore, the Clinical Research Sites may have certain existing legal obligations to the NIAID.

2.2 (b)(4)

2.3 The NIAID will use its best efforts to not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:

(i) Debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or

(ii) Suspended by the Office for Human Research Protections (OHRP) as a clinical research site under 45 C.F.R. Part 46, and

2.3.2 Any person convicted of a felony under federal law for conduct:

(i) Relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application (NDA), Biologics License Application (BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or

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(ii) Otherwise relating to the regulation of any drug product or medical device under the FD&C Act.

2.3.3 Any person performing services in connection with this Clinical Trial that has been disqualified as a clinical investigator under 21 C.F.R. Part 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required under 21 C.F.R. Part 312.53.

2.4 If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party immediately.

2.5 The NIAID shall use best efforts to confirm that Investigators, the Clinical Research Site, and other Clinical Trial personnel will, conduct the Clinical Trial in accordance with good clinical practice, including as defined by the ICH and comply with all applicable U.S. and foreign government, state and local laws, regulations and guidelines, including but not limited to those related to Human Subjects protection, Investigator qualifications, and Test Article where applicable.

2.6 The Parties agree that this Protocol will be conducted only at the Clinical Research Sites. However, the Company can conduct, at its own expense and under its own IND, additional clinical trials with the Test Article, including at the Clinical Research Site(s).

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND.** The NIAID will submit an IND covering the Protocol to the FDA. The IND will satisfy all of the requirements of the FDA and as applicable, will comply with eCTD format requirements. Company agrees to provide all requested documents for IND submission to NIAID in eCTD format. The Company will provide a letter granting the FDA permission to cross-reference the Company's pertinent Drug Master File (DMF), New Drug Application (NDA), Biologics License Application (BLA), and/or INDs in support of any required NIAID IND for the Clinical Trial, and in return, the NIAID will also provide a letter to the Company, if requested by the Company, granting the FDA permission to cross-reference any required IND filed by the NIAID for this Clinical Trial. The NIAID will promptly provide a copy of all IND submissions (together with any and all ancillary documents) to the Company for the Clinical Trial at the time they are submitted to the FDA.

3.2. **Protocol Monitoring.** The NIAID will be responsible for Clinical Research Site monitoring and quality assurance of all data in accordance with the clinical monitoring plan for the Clinical Trial. Monitoring will be done in compliance with FDA Good Clinical Practice Guidelines (ICH) (E6). The NIAID will communicate any clinically significant findings from clinical monitors to the Company in a timely manner.

3.3 **Safety Reporting**

3.3.1 Test Article safety definitions used in this Agreement shall be interpreted in accordance with Schedule 1 attached hereto and made a part hereof, in addition to those defined in Section 1 of this Agreement.

3.3.2 The NIAID will collect safety reports according to the procedure outlined in the Protocol. The NIAID will be responsible for the management of safety data from the Clinical Trial and any associated regulatory reporting obligations for individual or periodic safety reports to appropriate authorities (including the FDA), Investigators, and applicable IRBs, in compliance with all applicable laws, rules and regulations, and the requirements of the IRBs. Company agrees not to contact Clinical Research Sites directly for information related to Adverse Events. Company shall contact NIAID for information related to Adverse Events

3.3.3 For any safety events collected according to the Protocol that meet all of the following criteria of (i) Serious (ii) Unexpected and (iii) Suspected Adverse Reaction, NIAID will provide to the Company a completed copy of the IND safety report at the time the report is submitted to the FDA, NIAID will provide follow up information to Company at the time the follow up safety report is submitted to FDA. The reporting will be completed in the timeframes consistent with 21 CFR 312.32.

3.3.4 The NIAID will report all other safety events collected according to the Protocol not covered by 3.3.3 to the FDA and to the Company on a timely basis consistent with 21 CFR Part 312.33.

3.3.5 The NIAID will alert the Company's Pharmacovigilance and Epidemiology (PVE) at the address below of any potential safety issues or any Protocol amendments or changes to the Informed Consent Form for the Clinical Trial arising from a safety concern associated with any Company product within fifteen (15) calendar days of first becoming aware of such event.

3.3.6 The NIAID will report in English all safety information as defined below, which includes, but is not limited to:

3.3.6.1 all Serious Adverse Events (SAEs), in CIOMS I format, with respect to any Company product no later than 15 calendar days of first becoming aware of such events; and

3.3.6.2 (b)(4)

3.3.7 All safety reports addressed to the Company must be sent to the attention of the Company safety contact identified in Section 24 (Notices).

3.3.8 Upon the Company's request, and subject to any restrictions in applicable policies for the Clinical Trial, the NIAID will provide any additional information required to perform medical assessments of any safety information provided to the Company, including the provision of blinded data if applicable. Upon Company's request, and subject to any restrictions in applicable policies for the Clinical Trial, the NIAID will provide unblinding information for reports that are assessed as Serious and Unexpected Suspected Adverse Reactions (SUSARs). The NIAID will provide the Company all reasonable assistance in providing any further information requested by the Company. The Company will send any such request for additional information to the NIAID safety contact identified in Section 24 (Notices).

3.3.9 As the manufacturer of the Test Article, the Company will, in a timely manner consistent with FDA requirements and during the term of this Clinical Trial, provide the NIAID with any information regarding the safety and/or the toxicity of the Test Article that may impact Human Subject safety or Clinical Trial integrity as a safety letter communication. The NIAID will promptly transmit that information to all Investigators. All such reports or information to be submitted by the Company to the NIAID will be sent to to the NIAID safety contact identified in Section 24 (Notices).

3.3.10 The NIAID will be responsible for the preparation of any periodic safety reports required of NIAID for the Clinical Trial. For the avoidance of doubt, the Company does not wish to routinely receive copies of periodic safety reports. For this blinded Clinical Trial, the NIAID shall forward additional information after end of the Clinical Trial unblinding to Company as defined in Section 3.3.4 above.

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3.3.11. The NIAID will provide the Company with a copy of all reports submitted to government agencies that are related to the Clinical Trial and affect the Company or pertain to the Test Article in any manner (including but not limited to the IND annual report), as well as any correspondence with such authorities related to the Clinical Trial and affect the Company or pertain to the Test Article in any manner.

3.4 **Safety Monitoring.** In accordance with NIH guidelines, the Company and NIAID agree that the following type of safety monitoring is necessary and appropriate for this Clinical Trial:

3.5 Data Safety Monitoring Board (DSMB). The designated DSMB will be responsible for overseeing the outcome and safety data of this Clinical Trial on behalf of NIAID. The NIAID will notify Company at least five (5) business days in advance of each scheduled DSMB review and will promptly provide Company with any and all applicable reports and other information derived from each DSMB review. Furthermore, NIAID will promptly notify Gilead of any significant issues identified by the DSMB pertaining to the Company's Test Article and include Company in subsequent team meetings addressing DSMB concerns. The Company may participate in any or all open session reviews of the DSMB. The NIAID will use best efforts to confirm that recommendations from the DSMB are communicated promptly to the Company.

4. FDA MEETINGS/COMMUNICATIONS

4.1 If there are any discussions with the FDA involving data obtained from this Clinical Trial, the NIAID, in consultation with the Company, will take the initiative in arranging meetings or conference calls with the FDA. Formal meetings with the FDA concerning the Clinical Trial design and/or data will be discussed and agreed upon in advance by the Company and the NIAID. The Company will have the right to participate in all formal meetings with the FDA. The Company agrees not to contact the FDA independent of the NIAID concerning NIAID in this Clinical Trial.

(b)(4)

4.2 The Parties will promptly notify each other of:

4.2.1 any FDA correspondence related to the Test Article or Protocol that is received by the Company or its Affiliates, or the NIAID;

4.2.2 any FDA enforcement actions directed toward the Company or its Affiliates related to the Test Article, including but not limited to: warning letters, seizures, recalls, injunctions/consent decrees, rejection of regulatory submissions or withdrawal of approval for the Test Article:

4.2.3 any FDA enforcement actions directed toward NIAID related to the conduct of the Clinical Trial;

4.2.4 any criminal investigations related to the conduct of the Clinical Trial;

4.2.5 any proceedings to debar the Company or its Affiliates, or the NIAID or individuals providing services for the Clinical Trial employed under a contract to the Company and/or its Affiliates, or to the NIAID.

4.3 The Company will also promptly notify NIAID of any action taken by the FDA regarding manufacturing of the Test Article that would impact the safety of Human Subjects in the Clinical Trial.

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5. SUPPLY, DISTRIBUTION, AND USE OF TEST ARTICLE

5.1 **Supply**.

5.1.1 The NIAID will provide the Company with an estimate of the quantity of Test Article that will be required to complete the Protocol as set forth in this Agreement.

5.1.2 The Company will supply the Test Article to the NIAID (b)(4) (b)(4) and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Test Article.

5.1.3 The Company will be responsible for labeling the Test Article used in the Clinical Trial. NIAID will be responsible for review and approval of the label prior to Company labeling the Test Article. The NIAID will use best efforts to confirm that no other labels or label changes are made to the Test Article, unless made to the expiration date or storage conditions in accordance with the Company's advance written approval to NIAID or the Company's advance written instructions to the NIAID.

5.2 **Distribution.**

5.2.1 The Company will ship the Test Article to the Distributor as appropriate, on a schedule and in quantities as mutually agreed by the Parties. The Company will provide specific storage and/or shipping instructions for the Test Article to the NIAID and/or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. The Company warrants that any packaging for hazardous material provided by the Company meets Department of Transportation regulatory requirements for use at the Clinical Research Site to include provision of Material Safety Data Sheets for the Test Article.

5.2.2 The Test Article must be received by the Distributor, in usable condition and accompanied by Material Safety Data Sheet (MSDS), specific storage and shipping instructions, stability and/or expiration dating information and the finally signed and dated Certificate of Analysis (COA) for each lot of Test Article sent. The Company will also provide documentation to support the cGMP status of the Test Article. If the Company performs ongoing stability testing for each lot of Test Article sent, then the Company will also provide updated retest or expiration dates for those respective lots to NIAID in a timely manner.

5.2.3 If there is evidence that the Test Article that arrived at the Distributor, has not been delivered according to the defined shipping instructions or there is evidence of damage to the Test Article container or container closure system, NIAID and/or the Clinical Research Sites, will contact the Company to inform them of the condition of the received Test Article and to determine together with the Company whether the Test Article is usable or if it must be replaced. If the Test Article must be replaced, the Company will replace it at no cost to the Distributor.

5.3 **Use.**

5.3.1 (b)(4)

5.3.2 The NIAID will use best efforts to confirm that the Investigators:

(i) use the Test Article only in accordance with the Protocol and for no other purpose;
(ii) not transfer the Test Article to any parties except the Company; and
(iii) not chemically modify, replicate, make derivatives of, or reverse engineer the Test Article unless mutually agreed to in advance, in writing, by the Parties; and
(iv) comply with all applicable laws, rules and regulations.

5.4 **Investigator Brochure**. The Company will provide a current Investigator Brochure for all applicable components of the Test Article, and any later revisions and addenda to the Investigator Brochure for the Test Article to the NIAID, as mutually agreed by the Parties. The NIAID will keep the Investigator Brochure in confidence in accordance with Section 11 (Confidential Information) of this Agreement.

5.5 **Disposition of Unused Test Article.** (b)(4)

(b)(4)

5.6 **Warranty.** The Company represents and warrants that the Test Article supplied at the time of shipment shall be manufactured and released according to the principles of current Good Manufacturing Practice. EXCEPT FOR THE FOREGOING, COMPANY PROVIDES THE TEST ARTICLE "AS IS", WITH NO WARRANTY, EXPRESS OR IMPLIED OR STATUTORY, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY, TITLE, NON-INFRINGEMENT, EXCLUSIVITY OR FITNESS FOR A PARTICULAR PURPOSE.

5.7 **Post Clinical Trial Plan.** The NIAID agrees, and will use best efforts to confirm that the Clinical Research Sites and Investigator agree, that Company shall not be responsible for providing any Test Article or any other products or therapy to Human Subjects following their respective completion of the Clinical Trial.

6. PROTOCOL DEVELOPMENT AND REGISTRATION

6.1 Development and management of the Protocol, evaluation of data/results, proposal of amendments and recommendations for early termination shall be the responsibility of the Protocol Team.

6.2 The Parties agree that enrollment in the Clinical Trial will not start until the version of the Protocol to be used has been reviewed in advance by the Protocol Team; approved (stipulations met/resolved) by the relevant IRB(s) and the NIAID in writing; and submitted to the FDA under an existing IND, any FDA wait period has been satisfied, any FDA clinical hold issues have been responded to satisfactorily, and notification has been received by NIAID from the FDA that the Clinical Trial in the IND may begin. The Protocol is a product of NIAID and will be deemed NIAID Confidential Information, as defined in Section 11 (Confidential Information) of this Agreement, however Gilead shall be free to share the Protocol and any subsequent amendments thereto to the FDA and other regulatory agencies throughout the world. The Protocol will be posted to *ClinicalTrials.gov*, as required by DMID, NIAID, the Final Rule for FDAAA 801, issued in September 2016, and the NIH Policy on the Dissemination of NIH-funded Clinical Trial Information, also issued in September 2016.

6.3 (b)(4)

6.4 The NIAID, through its contractors or designees on behalf of NIAID, will be responsible for performing the randomization. NIAID will determine who will have access to the randomization

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codes; however, NIAID will provide Company with access to these codes in accordance with Section 9.8 below.

6.5 NIAID will register the Informed Consent Form and Protocol for the Clinical Trial.

7. CASE REPORT FORM DEVELOPMENT AND STATISTICAL ANALYSIS PLAN DEVELOPMENT

The NIAID or its designee on behalf of NIAID will be responsible for the development and subsequent revisions, if any, of the Case Report Forms and the statistical analysis plan for the Clinical Trial with appropriate review and comment by the Protocol Team prior to implementation.

8. HUMAN SUBJECTS PROTECTION

8.1 The NIAID and the Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The Informed Consent Form of each Human Subject participating in the Clinical Trial at a Clinical Research Site(s) will be obtained prospectively using an IRB approved informed consent process that complies with all applicable laws and regulations. (b)(4)
(b)(4)
(b)(4)

8.2 The NIAID and the Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46 and 21 C.F.R. Part 50, both concerning Protection of Human Subjects, and in a Certificate of Confidentiality issued by NIH in accordance with 42 U.S.C 241(d) of the Public Health Service Act.

Therefore:

8.2.1 Any ISI that Company receives from NIH is covered by a CoC and therefore all copies of ISI are immune from the legal process, and will not, without the consent of the Human Subject, be admissible as evidence or used for any purpose in any action, suit, or other judicial, legislative, or administrative proceeding.

8.2.2 The NIAID and the Company will maintain the confidentiality of ISI of Human Subjects collected under the Clinical Trial and protect the privacy of each of the individual Human Subjects in the Clinical Trial unless disclosure is required by law (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding. Prior to making any permitted disclosures, Company will ensure that any recipient of ISI protected by a CoC is aware of its confidential nature and the requirement to comply with the CoC..

8.2.3 The NIAID and the Company agree that neither Party will, nor will they allow their respective employees and contractors or any entity or person working on their behalf to, include ISI that could lead to identification of individual Human Subjects in any release of data, reports or publications related to the Clinical Trial. The NIAID will use best efforts to confirm that the Clinical Research Site and Investigators do not include ISI that could lead to identification of individual Human Subjects in any release of data, reports or publications related to the Clinical Trial.

8.2.4 The NIAID and the Company agree that neither Party will, nor will they allow their respective employees and contractors or any entity or person working on their behalf to, use

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ISI about Human Subjects for any purpose not stated in the Protocol without the consent of the Human Subject, the other Party, and local site IRB approval, unless such purpose is required or allowed by law. The NIAID will use best efforts to confirm that the Clinical Research Site and Investigators do not use ISI for any purpose not stated in the Protocol and Informed Consent Form without the written consent of the Human Subject, both Parties, and appropriate IRB approval, unless such purpose is required or allowed by law.

8.2.5 The NIAID and the Company agree to comply with the determinations of all IRBs overseeing the Clinical Trial. If a Party does not agree with a determination, the Parties will negotiate a mutually agreeable resolution.

8.2.6 Specimens and related data provided to the Company during and after the Clinical Trial will be encoded in accordance with applicable U.S., foreign government, state and local laws, regulations and guidelines. Unequivocally, neither IPI nor the key linking coded data to individuals will be released to the Company.

9. DATA ANALYSIS AND MANAGEMENT

9.1 Each Clinical Research Site will be responsible for the data and for scientific reporting of all results/data obtained from the Clinical Trial at an Investigator's Clinical Research Site, and submitting that data to the DCC.

9.2 The NIAID, and/or the Data Coordination Center (DCC) on behalf of NIAID, will have responsibility for all Clinical Trial data management, including but not limited to: collection, entry, and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

9.3 All data obtained from the Clinical Trial will be in the custody of Investigator or the Clinical Research Site, as applicable, which produces such data to the DCC. However, other than the Company, its contractors and its designees, NIAID will not allow a third party to review or use the data obtained from the Clinical Trial for purposes of seeking regulatory approval or any other commercial endeavor, unless the third party provides NIAID with advance written permission from the Company.

9.4 Within six (6) months after completion of the final data analysis for the Clinical Trial, or other period of time mutually agreed upon by the Parties, NIAID in collaboration with Company, as mutually agreed, will use best efforts to confirm that the DCC will provide to Company a copy of the draft Clinical Study Report for the Clinical Trial (b)(4)

(b)(4)

9.5 The NIAID is responsible for sending a final Clinical Study Report (or similar document) to the Company and the FDA as applicable, according to specified content no later than six (6) months after the Clinical Trial dataset is locked. All releases of data and reports from NIAID will be in accordance with applicable policies of releasing such data and reports.

9.6 Subject to the right of the NIAID and the Investigators to publish the data from this Clinical Trial as set forth in Section 10 (Publications and Press Releases) of this Agreement, the Company has the right to utilize the data reports (including, without limitation, the Clinical Study Report and data analysis set) from conducting this Clinical Trial for all legitimate business or regulatory purposes, including, without limitation, filing of IND applications and/or NDAs in the U.S. or their equivalents in other countries. The NIAID and/or the Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA, and the Securities and Exchange Commission (SEC) for all legitimate public health, regulatory or business purposes. (b)(4)

(b)(4)

9.7 Notwithstanding the foregoing, upon completion of the Clinical Trial, and at earlier times during conduct of the Clinical Trial where interim data or analysis is available, as described in the Protocol, NIAID will transfer or will authorize Clinical Research Sites to transfer to Company a copy of all data with such data or analysis set in a machine-readable or other format as requested by Company.

9.8 **Clinical Specimens for Use in Protocol.** All clinical specimens and isolates collected by the Investigators, or their staff, under this Clinical Trial are deliverables to NIAID under the Clinical Research Site Contract and shall remain in the custody of NIAID.

(b)(4)

9.9 (b)(4)

At the Company's request, and with the written approval of the DMID Program Officer and the DMID Project Officer, NIAID may, under a separate agreement, only when available and as permitted by the Informed Consent Form, (b)(4)

(b)(4)

10. PUBLICATIONS AND PRESS RELEASES

10.1 Except as specifically set forth in Section 10.3, any publications based on the results of the Clinical Trial and originating from NIAID, Investigators or the Clinical Research Site will conform to the applicable publication policy for the Clinical Trial. Unless requested otherwise by the Company, the NIAID will acknowledge the Company as the source of the Test Article in any NIAID publication resulting from the Clinical Trial and will use best efforts to confirm that the

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Investigators and the Clinical Research Site do the same in their publications resulting from the Clinical Trial.

10.2 Recognizing that employees of either Party may play an important role in the design, analysis, and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the generally accepted customs pertaining to authorship, and NIAID will use best efforts to confirm that the Investigators and the Clinical Research Site(s) include appropriate individuals from both Parties in the authorship of their publications resulting from the Clinical Trial.

Notwithstanding anything to the contrary in the applicable publication policies or elsewhere, each Party will provide, and the NIAID will use best efforts to confirm that the Investigators and the Clinical Research Site(s) will provide, the other Party with a copy of any abstract, oral presentation material, or manuscript prior to submission for publication or presentation, as applicable, with sufficient time [Abstracts and oral presentation materials: five (5) business days; Manuscripts: twenty five (25) business days] for review and comment. Each Party agrees that, following the receiving Party's review of the abstract, oral presentation material and/or manuscript for the maximum periods of time specified above, if no comment is received by the submitting Party, the submitting Party will be free to publish, present or use any Clinical Trial data. The receiving Party will maintain the proposed publication or public disclosure of the submitting Party as Confidential Information until publication or public disclosure by the submitting Party.

10.3 (b)(4)

10.4 Subject to the terms in NIAID's agreements or Awards with Clinical Research Sites, each Party will provide, and NIAID will use best efforts to confirm that Investigators and the Clinical Research Site will provide, a copy of any proposed press release to the other Party for review and comment at least five (5) calendar days in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, if no comment is received by the submitting Party and/or the Investigators or Clinical Research Sites, the submitting Party, Investigators, or Clinical Research Sites will be free to publish the press release.

11. CONFIDENTIAL INFORMATION

11.1 Either Party may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct the Clinical Trial. The disclosing Party will endeavor to place a confidentiality notice on all the Confidential Information. The disclosing Party will endeavor to reduce confidential non-written communications to writing within thirty (30) business days of first disclosure. Each Party receiving Confidential Information agrees that any information so designated will be maintained as Confidential Information in accordance with this Agreement and used by it only for the purposes of the Clinical Trial. Any Party may

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object to the designation of information as Confidential by the other Party. If such an objection is raised, the Parties agree to discuss and resolve that objection in good faith.

11.2 Unless expressly provided otherwise, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA), 5 U.S.C. § 552, 45 C.F.R. Part 5, or other applicable laws and/or regulations to disclose the Confidential Information, except that the NIAID may disclose the Company's Confidential Information to NIAID contractors and associates, and the Investigators, their respective IRBs, and other parties to the degree required for the conduct of the Clinical Trial. The NIAID will use best efforts to confirm that the Investigators and the Clinical Research Site(s) receiving the Company's Confidential Information maintain the confidentiality of Confidential Information consistent with the terms of this Agreement.

11.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. While the NIAID will endeavor to control the distribution of the Protocol document itself, the Company acknowledges that some Government documents are available (with abstracts) to the public under the Freedom of Information Act. In addition, NIAID policy requires posting of information and certain documents, including the Protocol and statistical analysis plan (SAP) be posted on the ClinicalTrials.gov registry of clinical studies, available through the NIH Website, consistent with the Food and Drug Administration Amendments Act of 2007, 121 STAT. 823. The NIAID shall be responsible for submitting all Clinical Trial information to Clinical Trails.gov.

11.4 Consistent with the NIH policy for sharing data obtained in NIH supported or conducted GWAS, NIAID is required to submit GWAS data to a central NIH database (database of Genotypes and Phenotypes (dbGaP)) in accordance with NIH policy, where it may be accessed by Investigators. All data submitted is coded and de-identified.

11.5 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given a reasonable opportunity to seek a court order to enjoin from disclosure.

11.6 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above or five (5) years after the expiration or termination date of this Agreement. Either Party may request an extension to this term when necessary to protect Confidential Information relating to the Test Article. This term does NOT apply to ISI, for which the obligation to maintain confidentiality will extend indefinitely.

12. INTELLECTUAL PROPERTY

12.1 Ownership of any Invention conceived solely or jointly by NIAID employees, the Clinical Research Site and Investigators, or other NIAID contractors or grantees as a consequence of conducting the Clinical Trial and involving the Test Article, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party acquires by virtue of this Agreement any right, title, nor interest in or to any issued Patents or pending patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by the Company to the NIAID.

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12.2 **NIAID Intellectual Property.**

12.2.1 The Government will retain title to any Patent, pending patent applications or other intellectual property rights in Inventions conceived solely by NIAID employees in the course of the Clinical Trial.

12.2.2 The NIAID agrees to notify the Company of any NIAID sole or joint Invention and to disclose it to the Company under an appropriate confidentiality agreement. The Company may apply for nonexclusive or exclusive license rights to any such patentable Invention made by NIAID employees that might arise during the Clinical Trial and the NIH will consider the Company's application for a nonexclusive or exclusive license consistent with 37 C.F.R. Part 404.

12.3 **Company Intellectual Property**. The Company will retain title to any Patents, pending patent applications, or other intellectual property rights in Inventions conceived by its employees during the course of the Clinical Trial.

12.4 **Clinical Research Site/Investigator Intellectual Property.**

This Agreement does not grant any license or obligation to license any intellectual property of the Clinical Research Sites or preclude the creation of intellectual property rights, including but not limited to Inventions conceived by the Investigators or other NIAID contractors or grantees during the course of the clinical research. The Company may enter into a separate agreement with the Clinical Research Site or Investigators, regarding intellectual property rights and confidentiality that do not interfere with the conduct of this Clinical Trial, contradict the terms of this Agreement or contradict the terms of the contract or grant award with NIAID.

12.5 **Joint NIAID-Company Intellectual Property.** The NIAID and the Company will have joint intellectual property rights in Inventions conceived jointly by their employees during the course of the Clinical Trial. Company may apply for a non-exclusive or exclusive license to the NIAID rights in such Inventions in accordance with the 37 CFR 404.

13. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

14. LIABILITY, INDEMNIFICATION, INSURANCE

14.1 **Liability.** In view of the Anti-Deficiency Act, 31 U.S.C § 1341, NIAID cannot agree to indemnify the Company for its losses. Each Party will be liable for the losses, claims, damages, or liabilities that it incurs as a result of its activities under this Agreement except that the NIAID, as an agency of the Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171.

14.2 **Indemnification.** The Company will defend, indemnify and hold harmless NIAID, and its grantees and contractors and their respective agents and employees associated with the Clinical Trial ("**Indemnitee(s)**") from any and all liabilities, damages, losses, claims, action, suits and expenses brought by a third party (excluding the cost of the time and effort of Indemnitees' own employees), including reasonable attorneys' fees and court costs (collectively "**Claims**") to the extent arising from injury or death to Human Subjects in the Clinical Trial for adverse drug experiences to Human Subjects caused in whole or in part by the manufacture, labeling, or

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packaging of the Test Article prior to shipment to the Distributor; provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if all of the following conditions are met:

14.2.1 The Claim was not proximately caused by the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, this Agreement, the agreements between the Clinical Research Site(s), Investigators, or other NIAID employees, contractors or grantees, all applicable laws, rules and regulations, and/or any written instructions from the Company;

14.2.2 The Claim was not caused by the negligence, recklessness or willful misconduct of any Indemnitee, provided that any action properly taken by the Indemnitee in compliance with written instructions from the Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if the injury or death giving rise to a Claim is jointly caused by the negligence of any Indemnitee and the administration or use of the Test Article in accordance with the Protocol, then Company will provide defense and indemnification only to the extent such injury or death was caused by the manufacture, labeling or packaging prior to shipment to the Distributor of the Test Article.

14.3 **Insurance**. The Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the Company's indemnification obligations described in Section 14.2 above. Upon request, the Company will provide evidence of its insurance or self-insurance to NIAID.

15. DISPUTES

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute through good faith negotiations within thirty (30) calendar days after notification thereof, the dispute will be referred to the Director of NIAID (or his/her designee) and an appropriate authorized representative of the Company for resolution. If the Director of NIAID (or his/her designee) and the authorized representative of the Company are unable to jointly resolve the dispute through good faith negotiations within thirty (30) calendar days, either Party may pursue any and all administrative or judicial remedies that may be available.

16. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the other Party, enter into any contract, warranty, or representation as to any matter. Neither Party will be bound by the acts of the other Party.

17. NON-ENDORSEMENT

By entering into this Agreement, the NIAID does not directly or indirectly endorse any product or service provided, or to be provided, by the Company. The Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However, the Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

18. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

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19. SURVIVABILITY

The provisions of Sections 1 (Definitions), 2 (Clinical Research Sites and Investigators), 3 (Investigational New Drug Application Sponsorship), 4 (FDA Meetings/Communications), 5 (Supply, Distribution, and Use of Test Article), 8 (Human Subjects Protection), 9 (Data Analysis and Management), 10 (Publications and Press Releases), 11 (Confidential Information), 12 (Intellectual Property), 14 (Liability, Indemnification, Insurance), 15 (Disputes), 16 (Independent Contractors), 17 (Non-Endorsement), 18 (Amendments), Section 19 (Survivability), and Section 23.4 (Term and Termination); will survive the expiration or earlier termination of this Agreement.

20. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement, provided that the confidentiality obligations contained in any prior agreement between the Parties and any confidentiality agreement entered into between the Parties shall continue in full force and effect in accordance with its terms. The provisions of this Agreement are severable and, in the event that any provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

21. ASSIGNMENT

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without the prior written consent of the other Party, except that the Company may assign this Agreement, with advance notice to NIAID, to its Affiliates or a successor-in-interest to its business through merger or consolidation, to which this Agreement pertains, provided that such successor assumes all obligations of the Company herein.

22. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

23. TERM AND TERMINATION

23.1 Unless terminated sooner in accordance with this Section 23, this Agreement will expire upon completion of the Clinical Trial and receipt of the Clinical Study Report by the Company.

23.2 The Parties may terminate this Agreement at any time by mutual written consent.

23.3 Either Party may unilaterally terminate this Agreement at any time by giving written notice at least thirty (30) calendar days prior to the desired termination date.

23.4 The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically appropriate. In that event, each enrolled Human Subject will be followed through the period outlined in the Protocol and the Company will supply enough Test Article to complete the Clinical Trial, without charge and on a schedule mutually agreed upon by the Parties to ensure the agreed upon supply of unexpired Test Article.

23.5 In the event the Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution, the Company must notify NIAID within at least thirty (30) calendar days of the dissolution.

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24. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt), or via facsimile, Portable Document Format (PDF), or email followed by conformational hard copies sent via courier when it is necessary to receive or deliver documents within a very short period of time [less than one (1) day].

For the Company:

For legal matters:
Gilead Sciences, Inc.
Attn: Corporate Legal Affairs
333 Lakeside Drive
Foster City, CA 94404
Fax: (b)(4)
E-mail: (b)(4)

For regulatory matters:
(b)(6) (b)(6)
Tel: (b)(6)
E-mail: (b)(6)@gilead.com

For technical matters:
(b)(6)
Tel: (b)(6)
E-mail: (b)(6)@gilead.com

For safety notices (including MedWatch reports and safety meeting information):

Gilead Sciences, Inc.
Pharmacovigilance and Epidemiology
333 Lakeside Drive
Foster City, CA 94404
Fax: 650.522.5477
Tel: 650.522.5114
E-mail: Safety_FC@gilead.com

For the NIAID:

John Beigel, M.D.,
Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases

For regulatory matters:
Janice Arega
Deputy Director, Office of Regulatory Affairs
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases

For information regarding safety and/or toxicity of the test article:
DMID Pharmacovigilance Group:
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Drive, Suite 650

Bethesda, MD 20817 U.S.A.

SAE Hot Line: 1-800-537-9979 (U.S.) or 1-301-897-1709 (outside U.S.)
SAE Fax Phone Number: 1-800-275-7619 (U.S.) or 1-301-897-1710 (outside U.S.)
SAE Email Address: PVG@dmidcroms.com
(for receipt of individual case safety reports and individual case acknowledgement)

All other notices:

DMID Agreement Coordinator
5601 Fishers Lane, Room 7F29 MSC 9826
Bethesda MD 20892-9826

SIGNATURES BEGIN ON THE NEXT PAGE

If the Company agrees with the terms of this Agreement for the Clinical Trial in accordance with the Protocol designated as DMID Protocol No. 20-0013, titled " A Multicenter Platform Trial of Putative Therapeutics for the Treatment of COVID-19 in Hospitalized Adults [Short Title: Big Effect Trial (BET)]" for remdesivir, please have an authorized representative sign below. This Agreement may be executed in counterparts, each of which shall be deemed an original, and all of which, when taken together, shall constitute one and the same instrument. A scanned electronic signature, or certified electronic signature, shall be as effective as the original signature.

FOR NIAID:

DocuSigned by:
Emily Erbelding
FDB80119125E43D...

8/17/2020
Date

Emily Erbelding, MD, MPH
Director, Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
5601 Fishers Lane
Room 7G51, MSC 9826
Rockville, MD 20852

FOR COMPANY:

(b)(6)

8/18/2020
Date

(b)(6)
(b)(6)
Clinical Research
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

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SCHEDULE 1

Abuse: Persistent or sporadic intentional excessive use of a medicinal product by a patient or clinical trial subject.

Adverse Reaction ("AR"): An untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or authorized medicinal product at any dose administered. Adverse Reactions may arise from Medication Errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), Misuse and Abuse of the product, Overdose or Occupational Exposure where applicable.

Development Safety Update Report ("DSUR"): A report providing an annual review and evaluation of pertinent safety information collected during the reporting period to summarize the current understanding and management of identified and potential risks, describe new safety issues that could impact clinical trial subjects and provide an update on the status of the development program.

Lack of Effect Report: A report of a situation where there is apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use. For avoidance of doubt, Lack of Effect reports from clinical trials refer to situations where the product is administered within the authorized indication and use.

Medication Error: Any unintentional error in the prescribing, dispensing or administration of a medicinal product while the medication is in the control of a healthcare professional, patient or consumer. Note: Medication errors may be classified as a) Medication Error without an AE, which includes situations of missed dose b) Medication Error with an AE, c) Intercepted Medication Error or d) Potential Medication Error.

Misuse: Use of a medicinal product that is intentional and inappropriate and not in accordance with its authorized product information.

Occupational Exposure: Exposure to a medicinal product as a result of one's professional or non-professional occupation.

Off-label Use: Where a medicinal product is intentionally prescribed by a Health Care Professional for a medical purpose not in accordance with the authorized product information with respect to indication, route, dose or patient population (e.g. the elderly). For avoidance of doubt, Off-Label Use will not apply in clinical trials.

Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per the protocol or in the product labelling. The Parties agree that in the course of conducting a clinical study, the terms of the clinical study protocol (as fully approved by all applicable bodies) overrides the local product labelling.

Pregnancy Reports: Reports of pregnancy following maternal or paternal exposure to the product.

Product Complaints: Complaints arising from potential deviations in the manufacture, packaging or distribution of the medicinal product.

Special Situation Reports ("SSR"): One of a) Pregnancy, b) Abuse, c) Medication Error, d) Misuse, e) Off-Label Use, f) Overdose, g) Lack of Effect, h) AEs in infants following exposure from breastfeeding, i) AEs associated with Product Complaints or arising from Occupational Exposure. For the avoidance of doubt this applies to all reports including reports in a pediatric or elderly population.

NOTE: This is not an exhaustive list and any safety information should be reported to Company's PVE.

CONFIDENTIAL DISCLOSURE AGREEMENT

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, National Institute of Allergy and Infectious Diseases ("NIAID"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS"), and **Eli Lilly and Company** ("**Eli Lilly**") (each a "Party" and collectively, the "Parties"), intending to be legally bound as of the date of the last signature hereto ("Effective Date"), agree that:

1. A Party ("Disclosing Party") may disclose information to the other ("Receiving Party") for the purpose of discussing a proposed collaboration on Eli Lilly's monoclonal antibodies for treatment of SARS CoV-2 ("Purpose"). The Disclosing Parties are: NIAID and Eli Lilly.

2. The information disclosed under this Agreement ("Confidential Information") is described as: any and all information associated with Eli Lilly's anti-Sars-CoV-2 monoclonal antibodies.

3. The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its employees, investigators from the AIDS Clinical Trials Group (ACTG), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Cardiothoracic Surgical Trials Network (CSTN), Prevention and Early Treatment of Acute Lung Injury (PETAL), and the U.S. Department of Veterans Affairs (VA), consultants or contractors to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information.

4. The Receiving Party's duties under this Agreement shall apply to any Confidential Information shared orally or in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked "Confidential." Regarding oral disclosures of Confidential Information, if a Party does not reduce oral Confidential Information to writing, the Party must verbally provide notice of the confidential nature of the oral disclosure at the time it is disclosed for the oral Confidential Information to be considered confidential under this Agreement.

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the

Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure in the possession of the Receiving Party; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party, without reference to the information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return all Confidential Information received.

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required to disclose any of the Confidential Information, the Receiving Party shall provide the Disclosing Party with timely notice and, to the extent practicable, consult with the Disclosing Party prior to any disclosure.

8. This Agreement is made under and shall be construed in accordance with Federal laws as applied by the Federal Courts in the District of Columbia, and constitutes the entire understanding between the Parties with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for three (3) years from the Effective Date.

9. Notices or other communications required to be sent to NIAID under this Agreement shall be sent in writing and addressed to Technology Transfer & Intellectual Property Office, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Ste 6D Rockville, MD 20852. Notices required to be sent to Eli Lilly under this Agreement shall be in writing and addressed to (b)(6) Advisor, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, with copy to General Counsel, Eli Lilly and Company.

10. Each Party has caused this Agreement to be executed on its behalf in duplicate (each of which duplicate shall be deemed to be an original).

REMAINDER OF PAGE INTENTIONALLY LEFT BLANK

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Institute of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH)
5601 Fishers Lane, Ste 6D
Rockville, MD 20852

Authorized Signature:

Wade W. Green -S Digitally signed by Wade W. Green -S
Date: 2020.06.19 08:40:54 -04'00'

Wade Green, Ph.D.
Acting Deputy Director, Technology Transfer & Intellectual Property Office

Date (Month/Day/Year): 19 June 2020

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Authorized Signature:

(b)(6)

Name: (b)(6)
Title: (b)(6)

Date (Month/Day/Year): 06/19/2020

Amendment Number One to Confidential Disclosure Agreement # 2020-0896

This Amendment Number One ("Amendment One") to the Confidential Disclosure Agreement (the "Agreement"), effective June 19, 2020, between National Institute of Allergy and Infectious Diseases ("NIAID"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS"), and Eli Lilly and Company ("Eli Lilly") to protect confidential information related to information associated with Eli Lilly's anti-Sars-CoV-2 monoclonal antibodies.

The purpose of this Amendment One is to modify Article 3 of this Agreement. This change is reflected below, and except for this change, all other Articles of the original Agreement remain in full force and effect.

WHEREAS, the parties desire to amend the Agreement as set forth herein:

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged and intending to be legally bound, the parties hereto agree as follows (deletions in ~~strikeout~~, additions in underline):

1. **Article 3:**

   The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its employees, investigators from the AIDS Clinical Trials Group (ACTG), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Cardiothoracic Surgical Trials Network (~~CSTN~~CTSN), Prevention and Early Treatment of Acute Lung Injury (PETAL), employees of National Heart, Lung, and Blood Institute (NHLBI) involved in the oversight and management of CTSN and PETAL, employees of the Foundation for the National Institutes of Health (FNIH) involved the ACTIV program, and the U.S. Department of Veterans Affairs (VA), consultants or contractors to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information.

This Amendment One may be executed in counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. A facsimile, scanned electronic signature or certified electronic signature shall be as effective as an original signature.

IN WITNESS WHEREOF, each party has caused this Amendment One to Agreement to be executed by its authorized representative.

FOR NIAID

Wade W. Green -S Digitally signed by Wade W. Green -S Date: 2020.07.02 14:33:08 -04'00'

Date: 02 July 2020

Wade Green, Ph.D.
Lead Technology Transfer and Patent Specialist
Technology Transfer and Intellectual Property Office (TTIPO)
National Institute of Allergy & Infectious Diseases, NIH

For Eli Lilly

(b)(6)

Date: July 6, 2020

Name: (b)(6)
Title: (b)(6)

Reviewed as to legal form: TLC

IND SPONSOR: NIAID (DAIDS)

CLINICAL TRIAL AGREEMENT

BETWEEN

DIVISION OF AIDS (DAIDS), NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

&

ELI LILLY AND COMPANY

Based on

Protocol ACTIV-2/A5401

Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

The **National Institute of Allergy and Infectious Diseases ("NIAID")**, an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services (HHS), as represented by the **Division of AIDS ("DAIDS")** and **Eli Lilly and Company** (the "Company"), located at Lilly Corporate Center, Indianapolis, IN 46285 (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial designated as Protocol **ACTIV-2/A5401**, entitled "**Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)**."

This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). NIAID (DAIDS) will conduct this Clinical Trial through NIAID (DAIDS) extramurally funded AIDS Clinical Trials Group (ACTG) Clinical Research Sites under the terms of their Grant/Cooperative Agreement with NIAID (DAIDS). In the event that non-ACTG Clinical Research Sites funded by NIAID (DAIDS) are included in this Clinical Trial in order to complete enrollment, these sites will meet NIAID (DAIDS) standards for clinical research sites conducting research sponsored by NIAID (DAIDS). The Clinical Research Sites and their respective Investigators are not parties to this Agreement.

This Agreement sets forth the terms and conditions under which this Clinical Trial will be conducted and managed.

Company and NIAID (DAIDS) agree as follows:

1. DEFINITIONS

The terms listed in this Section will carry the meanings indicated throughout this Agreement. To the extent that a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code ("U.S.C.") or the Code of Federal Regulations ("C.F.R."), the definition in the U.S.C. or C.F.R. will control.

"**ACTG**" means the AIDS Clinical Trials Group network sponsored and funded by NIAID (DAIDS) in accordance with the terms of a Cooperative Agreement.

"**Adverse Event**" or "**AE**" will be defined per the Protocol.

"**Affiliate**" means, with respect to Company, (i) any legal entity of which the securities or other ownership interests representing fifty percent (50%) or more of the equity or fifty percent (50%) or more of the ordinary voting power or fifty percent (50%) or more of the general partnership interest are, at the time such determination is being made, owned, controlled, or held, directly or indirectly, by such legal entity; or (ii) any legal entity which, at the time such determination is being made, is controlling or under common control with, such legal entity. As used herein, the term "control," whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract, or otherwise.

"**Agreement**" means this Clinical Trial Agreement ("**CTA**"), all executed amendments and supplements to this Agreement, and all schedules, appendices and/or addenda to this Agreement.

"**Case Report Form**" or "**CRF**" means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Clinical Research Sites**" means the clinical research sites designated as the ACTG sites and any other sites where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Trial**" means a biomedical or behavioral research study of Human Subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments or devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. In this Agreement, Clinical Trial means the clinical trial for the Protocol.

"**Confidential Information**" means confidential scientific, proprietary, business and/or financial information, provided that Confidential Information does not include:

(a) Information that is in the public domain or subsequently enters the public domain through no fault of the receiving Party;

(b) Information that is presently known or becomes known to the receiving Party from its own independent sources, without restriction as to confidentiality or use, from a person having the legal right to disclose the data;

(c) Information that can be established by competent proof was already known and lawfully in the possession of the receiving Party at the time of the disclosure, without restriction as to confidentiality or use;

(d) Information that is independently created or compiled by the receiving Party without reference to or use of the Confidential Information and such independent development can be documented by receiving Party with written records;

(e) Information that is reasonably required by scientific standards for publication of the results of the Clinical Trial (including Clinical Trial methods and/or data) or any information that is necessary for other researchers to verify the results of the Clinical Trial;

(f) Information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Study Product; or

(g) Information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, or required to be disclosed by a court of competent jurisdiction or governmental authority, provided that the Party required to disclose provides the other Party with prompt written notice and an opportunity (if legally permissible) to obtain a protective order.

"**Critical Event**" means any unanticipated study-related incident that is likely to cause or increase the risk of harm to participants or others or has a significant adverse impact on

study outcomes or integrity.

"**Data and Safety Monitoring Board**" or "**DSMB**" means an independent group of experts that advises NIAID (DAIDS) and the Investigators. The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (2) make recommendations to NIAID (DAIDS) concerning the continuation, modification, or termination of the Clinical Trial.

"**Distributor**" means the NIAID (DAIDS) contractor who will be distributing the Study Product to the Clinical Research Sites. The Distributor for this Clinical Trial is the Clinical Research Products Management Center ("**CRPMC**").

"**Effective Date**" means the date of the last signature of the Parties executing this Agreement.

"**Electronic Common Technical Document**" or "**eCTD**" means the standard format for electronic regulatory submissions as per 21 U.S.C. § 379k-1, "Electronic Format for Submissions," and as further described in FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," 80 Federal Register 26057 (2015).

"**FDA**" means the U.S. Food and Drug Administration.

"**Government**" means the Federal Government of the United States of America.

"**Grant/Cooperative Agreement**" means the award providing financial assistance from NIAID (DAIDS) for approved activities. In a Grant, performance responsibility rests primarily with a grantee with little or no government involvement in the research. A NIAID (DAIDS) Cooperative Agreement is a Grant in the U series that features substantial NIAID (DAIDS) scientific involvement.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. § 46.102(e)(1), a living individual about whom an Investigator conducting research:

(a) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimen; or

(b) Obtains, uses, studies, analyzes or generates Identifiable Private Information or identifiable biospecimens.

"**ICH**" means the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Cited are:
ICH E3: "Structure and Content of Clinical Study Reports."
ICH E6: "Good Clinical Practice: Consolidated Guidance," published in the Federal Register [83 Federal Register 8882 (2018)]. Also referred to as "FDA Good Clinical Practice Guidelines."

"**Identifiable Private Information**" or "**IPI**" about a Human Subject means private information from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**IND**" means an "**Investigational New Drug Application**," filed in accordance with 21 C.F.R. Part 312, under which clinical investigation of an experimental drug or biologic (Study Product) is performed in Human Subjects in the U.S., or intended to support a U.S. licensing action.

"**Institutional Review Board**" ("**IRB**") or "**Independent Ethics Committee**" ("**IEC**") means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects, and 21 C.F.R. Part 56, Subpart C: IRB Functions and Operations, as amended April 1, 2013, and other applicable regulations, an independent body comprising medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of the Human Subjects involved in a clinical trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**Invention**" means any invention or discovery that is or may be patentable or otherwise protectable under Title 35 of the U.S.C.

"**Investigator**" means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Study Product to a Human Subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, Investigator means the individual(s) identified as responsible for the conduct of the Clinical Trial at the designated ACTG Clinical Research Sites.

"**Investigator's Brochure**" or "**IB**" means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Study Product, including animal screening, preclinical toxicology and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the Study Product or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Study Product.

"**Office for Human Research Protections**" or "**OHRP**" means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"**Patent**" means any issued U.S. patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

"**PPD**" means Pharmaceutical Product Development, Inc., a contract research organization responsible for monitoring the Clinical Trial, under contract to NIAID (DAIDS).

"**Product Quality Complaint**" or "**PQC**" means any written, electronic, or oral communication that states possible deficiencies in the Study Product that may involve failure to meet any of its specifications (e.g., identity, quality, purity, durability or reliability), including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the Study Product.

"**Protected Health Information**" or "**PHI**," as defined in 45 C.F.R. Parts 160 and 164, under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), includes any *individually identifiable* health information. *Identifiable* refers not only to data that is explicitly linked to a particular individual; it also includes health information with data items which reasonably could be expected to allow individual identification.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV-2/A5401, "Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)." The Protocol describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. The Agreement will be governed by the most recent version of the Protocol, and should the Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement, the terms of the Agreement will govern.

"**Protocol Team**" means the team responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. The Protocol Team will include the protocol chair (an Investigator), representatives from Company, other Investigators, representatives from NIAID (DAIDS), and the persons involved with statistical and data analysis for the Clinical Trial. Participation on the Protocol Team will be as agreed by the Parties and will take into account any special requirements of the Protocol design.

"**Regulatory Support Center**" or "**RSC**" means the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory activities related to NIAID (DAIDS)'s clinical research. The RSC is part of Technical Resources International, Inc. (TRI), and operates pursuant to a contract between TRI and NIAID (DAIDS).

"**Sponsor**" means, in accordance with the definition in 21 C.F.R. § 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with Study Product. For the purposes of this Agreement, "Sponsor" is referred to as the IND holder.

"**Statistical and Data Management Center**" or "**SDMC**" means the data management center responsible for providing statistical and data management services for ACTG clinical trials, including the Clinical Trial that is the subject of this Agreement in accordance with the terms of a cooperative agreement with NIAID (DAIDS).

"**Study Product**" means, in accordance with 21 C.F.R. § 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301, *et seq*., Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended. In this Agreement, LY3819253 is referred to as the Study Product.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 Company acknowledges that NIAID (DAIDS) funds the Clinical Research Sites under a Grant/Cooperative Agreement, and therefore, the Clinical Research Sites have certain existing contractual or other legal obligations to NIAID (DAIDS).

2.2 Company will not provide any funding or material for any aspect of the Clinical Trial to any Clinical Research Site participating in the Clinical Trial without prior written notification to NIAID (DAIDS). In addition, subject to Section 14.4 of this Agreement, Company will not enter into any separate agreements, including, but not limited to, material transfer agreements, with the Clinical Research Sites or the Investigators at the Clinical Research Sites that interfere with the conduct of this Clinical Trial.

2.3 NIAID (DAIDS) hereby certifies that it did not and will not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:
- (i) debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or
- (ii) suspended by OHRP as a clinical research site under 45 C.F.R. Part 46.

2.3.2 Any person convicted of a felony under federal law for conduct:
- (i) relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application (NDA), Biologics License Application (BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or
- (ii) otherwise relating to the regulation of any drug product or medical device under the FDCA.

2.3.3 Any person performing services in connection with this Clinical Trial who has been disqualified as a clinical investigator under 21 C.F.R. § 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required by 21 C.F.R. § 312.53.

2.4 If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party immediately.

2.5 The Grant/Cooperative Agreement requires that the Investigators at Clinical Research Sites conduct the Clinical Trial in accordance with applicable provisions of ICH E6: FDA Good Clinical Practice Guidelines, and requires that they comply with all applicable U.S., foreign government, state and local laws, regulations and guidelines.

2.6 Company agrees that this Protocol will be conducted only at sites as defined in the Protocol. However, Company can conduct, at its own expense and under its own IND, additional clinical trials with the Study Product, at non-NIAID (DAIDS) funded sites. Company agrees to inform NIAID (DAIDS) in writing of any other clinical trials it may support for the use of the Study Product that would compete with this Clinical Trial for the same Human Subject population.

2.7 If Protocol-specified assays expected to be included in a regulatory submission are performed in laboratories not monitored by NIAID (DAIDS), Company warrants that such laboratories will comply with applicable Good Clinical Laboratory Practice (GCLP) and all applicable regulatory requirements. Company will provide NIAID (DAIDS) with results of such assays and, upon request, provide documentation to support that the testing and laboratory operations are compliant with applicable GCLP and all applicable regulatory requirements. NIAID (DAIDS), through its contractor, may audit the laboratory(ies) to ensure compliance with applicable GCLP and all applicable regulatory requirements.

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND.** NIAID (DAIDS) will submit an IND covering the Protocol to the FDA. The IND will satisfy all of the requirements of the FDA, and, as applicable, will comply with eCTD format requirements. Company agrees to provide all requested documents to NIAID (DAIDS) in eCTD format. Company will provide a letter granting the FDA permission to cross-reference Company's pertinent Master File (MF), New Drug Application (NDA), Biologics License Application (BLA), and/or INDs in support of the NIAID (DAIDS)'s IND, and in return, NIAID (DAIDS) will also provide a letter to Company, if requested, granting the FDA permission to cross-reference the IND filed by NIAID (DAIDS) for this Clinical Trial. NIAID (DAIDS) will provide a copy of all IND submissions to Company at the time they are submitted to the FDA. Any Confidential Information of another party will be removed.

3.2 **Clinical Research Site Monitoring.** NIAID (DAIDS), through PPD, will be responsible for Clinical Research Site monitoring in accordance with the clinical monitoring plan. Monitoring will be done in compliance with applicable provisions of the FDA regulations. NIAID (DAIDS) will communicate any Critical Event findings from clinical monitors to Company in a timely manner.

3.3 Adverse Event Reporting.

3.3.1 NIAID (DAIDS) will collect Adverse Event reports according to the procedure outlined in the Protocol and in accordance with 21 C.F.R. § 312.32. The Clinical Research Sites will report Adverse Events to NIAID (DAIDS) in a timely manner and in accordance with procedures outlined in the Protocol and in accordance with 21 C.F.R. § 312.32. NIAID (DAIDS) will assume responsibility for the reporting of Adverse Events to the FDA and will provide copies of all of the safety reports to Company.

3.3.2 NIAID (DAIDS) will report all unexpected Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the FDA and Company on a timely basis consistent with 21 C.F.R. § 312.32 and the Protocol. NIAID (DAIDS) will report other serious and non-serious adverse events to the FDA and to Company on a timely basis consistent with 21 C.F.R. § 312.33. NIAID (DAIDS), through PPD, will report all Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the Company at the Safety Reports Address listed in the Contacts section within fifteen (15) days of PPD receiving the SAE. Company agrees not to contact the Clinical Research Sites directly for information related to Adverse Events. Company shall contact the following for information related to SAEs:

(b)(6)
Project Management
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

(b)(6)
PVG Manager
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

3.3.3 As the manufacturer, Company will, in a timely manner consistent with FDA requirements and during the term of this Clinical Trial, provide NIAID (DAIDS) with any information it now has or may obtain in the future regarding the safety and/or the toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial. NIAID (DAIDS) will promptly transmit that information to all Investigators. Such information shall be sent to:

(b)(6)
Project Management
PPD

E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

(b)(6)
PVG Manager
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

3.3.4 During the course of the study, if Company is requested by a regulatory agency to unblind an SAE report, NIAID (DAIDS) will collaborate with Company to determine whether the report can be unblinded without undermining the scientific integrity of the Clinical Trial. NIAID (DAIDS) will provide the blinding codes for study subjects randomized to the Study Product or the placebo to Company when all data forms have been keyed into the database for all subjects, data cleaning has been completed, and the Protocol Team has declared the study data set to be complete.

4. SAFETY MONITORING

Data and Safety Monitoring Board (DSMB). A NIAID (DAIDS) DSMB will monitor this Clinical Trial as described in the Protocol. NIAID (DAIDS) will notify Company in advance of any DSMB review. NIAID (DAIDS) will provide recommendations derived from the DSMB to Company.

5. FDA MEETINGS/COMMUNICATIONS

5.1 With respect to any discussions with the FDA involving data obtained from this Clinical Trial under NIAID (DAIDS)'s IND, NIAID (DAIDS), in consultation with Company, will take the initiative in arranging meetings or conference calls with the FDA. Formal meetings with the FDA concerning the Clinical Trial design and/or data will be discussed and agreed upon in advance by Company and NIAID (DAIDS). Company will have the right to participate in all formal meetings with the FDA. Company agrees not to contact the FDA independently of NIAID (DAIDS) concerning this Clinical Trial. However, Company may contact the FDA on separate product-related issues. NIAID (DAIDS) will provide Company with copies of all transmittal letters for IND submissions, and formal questions and responses that have been submitted to the FDA. Any Confidential Information of another party will be removed.

5.2 Company will promptly notify NIAID (DAIDS) of:

(a) Any FDA correspondence related to the Protocol that is received by Company, or its Affiliates; and
(b) FDA enforcement actions directly related to the Protocol or the Study Product directed toward Company or its Affiliates, including, but not limited to, warning

letters, seizures or recalls; injunctions/consent decrees; rejection of regulatory submissions or withdrawal of approval for a product; and

(c) Criminal investigations; and

(d) Proceedings to debar Company or its Affiliates or individuals employed under a contract to Company and/or its Affiliates.

5.3 Company will also promptly notify NIAID (DAIDS) of any action taken by the FDA regarding manufacturing of the Study Product that would impact the safety of Human Subjects in the Clinical Trial.

6. SUPPLY, DISTRIBUTION AND USE OF STUDY PRODUCT

6.1 **Supply.** NIAID (DAIDS) shall provide Company with an estimate of the quantity of Study Product that will be required to complete the Protocol. Company will supply the Study Product to NIAID (DAIDS) without charge and in quantities and conditions sufficient to complete the Protocol and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Study Product. Company will be responsible for labeling the Study Product used in the Clinical Trial.

6.2 **Distribution.**

6.2.1 Company will ship the Study Product to the CRPMC, as mutually agreed by the Parties. Company will provide specific storage and/or shipping instructions for the Study Product to NIAID (DAIDS), who will be responsible for adhering to them, as mutually agreed by the Parties. Company warrants that any packaging for hazardous material, provided by Company, meets Department of Transportation regulatory requirements for use at all Clinical Research Sites, if applicable. Incoterms to be delivery at place 2020.

6.2.2 The Study Product must be received by the CRPMC in usable condition and accompanied by Material Safety Data Sheet (MSDS), specific storage and shipping instructions, stability and/or expiration dating information, Certificate of Analysis (CoA) and the Certificate of Compliance (CoC).

6.2.3 If there is evidence that the Study Product that arrived at the CRPMC or Clinical Research Sites has not been maintained according to the defined shipping instructions, or is potentially adulterated, NIAID (DAIDS) will contact Company to inform it of the condition of the received Study Product and to determine if the Study Product is usable or if it must be replaced. If the Study Product must be replaced, Company will replace it at no cost to NIAID (DAIDS) or the Clinical Research Sites.

6.3 **Use.** NIAID (DAIDS) will not transfer the Study Product to parties other than the CRPMC or the Clinical Research Sites, nor will NIAID (DAIDS) chemically modify, replicate, make derivatives of or reverse engineer the Study Product unless mutually agreed in writing by the Parties. NIAID (DAIDS), pursuant to the Grant/Cooperative

Agreement, will ensure that the Investigators: (i) use the Study Product only in accordance with the Protocol and for no other purpose; (ii) do not transfer the Study Product to any parties except Company, the CRPMC or the Clinical Research Sites; and (iii) do not chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed to, in writing, by the Parties.

6.4 **Product Quality Complaints (PQCs).** All initial Product Quality Complaints (PQCs) involving the Company Study Product under study must be reported to Company by NIAID (DAIDS) within two (2) business day after being made aware of the event. The Company Study Product should be quarantined immediately, and if possible, a picture should be taken.

If the defect for the Company Study Product under study is combined with either a serious adverse event or non-serious adverse event, NIAID (DAIDS) shall report the PQC to Company according to the serious adverse event reporting timelines or the adverse event reporting timelines, as applicable.

6.5 **Study Product Return.** Upon completion of the Protocol, NIAID (DAIDS), through CRPMC, will destroy or, at Company's request, return any unused Study Product to Company.

6.6 **Warranty.** Company represents and warrants that the Study Product supplied meets the specifications cited in the CoA and CoC provided.

6.7 **Source.**

6.7.1 In the event Company elects to terminate its development of Study Product for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to NIAID (DAIDS) within ninety (90) days of discontinuation, then Company will provide NIAID (DAIDS) with Study Product sufficient to complete the Clinical Trial in the manner described in the Protocol.

6.7.2 The Parties also agree that should this Agreement be terminated prior to completion of the Protocol, the Protocol will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol and Company will supply enough Study Product to complete the Protocol.

7. INVESTIGATOR'S BROCHURE (IB)

Company will provide a current IB in eCTD format for all applicable components of the Study Product, and any later revisions and addenda to the IB for the Study Product, including a summary of changes (SOC), to NIAID (DAIDS), as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Section 13 (Confidential Information) of this Agreement. Company agrees to provide NIAID

(DAIDS) any updated version of the IB, with the SOC, within fifteen (15) days of issuance. Company will send the IB and SOC to:

(b)(6)
Project Management
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

(b)(6)
PVG Manager
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

NIAID (DAIDS), through PPD, will distribute the IB to the Clinical Research Sites. NIAID (DAIDS) will address requests for IBs, including updated versions and SOCs, to:

(b)(6)
(b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Phone: (b)(6)
E-mail: (b)(6) @lilly.com

8. PROTOCOL DEVELOPMENT AND REGISTRATION

8.1 The Parties agree that enrollment in the Clinical Trial will not start until the version of the Protocol to be used has been reviewed in advance by Company, accepted by the Protocol Team, approved by the relevant IRB(s)/IEC(s) and NIAID (DAIDS) in writing, submitted to the FDA, and any clinical hold issues have been responded to satisfactorily.

8.2 The Parties agree that any alteration in or amendment to the Protocol must be accepted by the Protocol Team, approved in writing by the relevant IRB(s)/IEC(s) and NIAID (DAIDS), and submitted to the FDA prior to such alteration or amendment becoming effective.

8.3 **Protocol Registration.** All NIAID (DAIDS)-sponsored network protocols which include the informed consent must meet all federal mandates as well as NIAID (DAIDS) requirements to ensure the welfare of Human Subjects in the Clinical Trial.

Each Clinical Research Site, prior to participating in any NIAID (DAIDS)-sponsored study, must submit its informed consent to the NIAID (DAIDS) Protocol Registration Office, c/o Regulatory Support Center (RSC), Technical Resources International, Inc.,

6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817. Attached is the latest version of the Protocol Registration Manual (see Addendum I).

9. CASE REPORT FORM DEVELOPMENT

NIAID (DAIDS), through the SDMC, will be responsible for the development and subsequent revisions, if any, of the Case Report Forms with appropriate review and comment by the Protocol Team.

10. HUMAN SUBJECTS PROTECTION

10.1 NIAID (DAIDS) and Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The informed consent of each Human Subject participating in the Clinical Trial at a Clinical Research Site will be obtained prospectively using an informed consent process. The sample informed consent document may be reviewed in advance by Company and shall be approved by NIAID (DAIDS) and all appropriate IRB(s)/IEC(s).

10.2 NIAID (DAIDS) and Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46, Protection of Human Subjects. Therefore:

10.2.1 NIAID (DAIDS) and Company will maintain the confidentiality of IPI, including PHI, collected under the Clinical Trial and protect the privacy of the individual Human Subjects unless disclosure is required by law.

10.2.2 NIAID (DAIDS) and Company may inspect, but not copy, Human Subjects' medical records that might also include information not directly connected to this Clinical Trial. However, NIAID (DAIDS) and Company agree that this information will remain confidential and will not be used for any purpose other than confirmation of Clinical Trial data or to resolve study-related injury issues.

10.2.3 NIAID (DAIDS) and Company agree that neither Party will use, nor will it allow its contractors to use, IPI for any purpose not stated in the Protocol, without the consent of the other Party and local site IRB/IEC approval unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative. NIAID (DAIDS) will ensure that the Investigators do not use IPI for any purpose not stated in the Protocol and informed consent document without the written consent of both Parties and appropriate IRB/IEC approval, unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative.

10.2.4 NIAID (DAIDS) and Company agree to comply with the determinations of all IRB(s)/IEC(s) overseeing this research.

10.2.5 Biospecimens and data related to biospecimens provided to Company during and after the Clinical Trial will be coded.

11. DATA COLLECTION, ANALYSIS AND MANAGEMENT

11.1 The Clinical Research Sites will be responsible for gathering the data and submitting it to the SDMC. The Protocol Team, which includes Company representatives, will be responsible for the scientific reporting of the data.

11.2 NIAID (DAIDS), through the SDMC, will have responsibility for the data management: collection, entry and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

11.3 In accordance with NIH Grants Policy, data obtained from the Clinical Trial is the property of the Investigator or the Clinical Research Site, as applicable which produces the data. However, other than Company, its contractors and its designees, any party wanting to review or use the data obtained from the Clinical Trial for purposes of seeking regulatory approval of the Study Product will obtain the prior written permission of Company.

11.4 Within thirty (30) days after providing the final statistical report, NIAID (DAIDS) will authorize the SDMC to transfer to Company a copy of the complete data analysis set from the Study Product and concurrently randomized placebo study arms in a machine-readable format to be determined jointly by the Parties. If Company requires that the data be provided in a customized format(s), Company will pay for all costs associated with the customized data format(s).

11.5 Subject to the right of NIAID (DAIDS) and the Investigators to publish the data from this Clinical Trial as set forth in the Publications and Press Releases Section of this Agreement, Company has the right to utilize the data reports and associated data from this Clinical Trial in its possession for all legitimate business or regulatory purposes. NIAID (DAIDS) and/or Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA and the Securities and Exchange Commission (SEC), for all legitimate public health, regulatory or business purposes. Except for information related to regulatory or safety issues or under emergency circumstances where it is not practicable to do so and to the extent permitted by law, NIAID (DAIDS) will not release information regarding the Clinical Trial to governmental organizations without prior notification to Company.

11.6 NIAID (DAIDS), through its contractor, will be responsible for preparing the final Clinical Study Report in accordance with ICH E3, “Structure and Content of Clinical Study Reports” and will provide a copy of the Clinical Study Report for the Company

Study Product to Company. NIAID (DAIDS) will provide such Clinical Study Report in draft form for Company's review prior to its finalization. The provision of such Clinical Study Report to Company by NIAID (DAIDS) is not conditioned upon the graduation of the Study Product.

11.7 Following review by the DSMB of study data through study day 28 in Phase II of the Clinical Trial and receipt by NIAID (DAIDS) of the DSMB's recommendations concerning graduation or otherwise of the Study Product from Phase II to Phase III evaluation, NIAID (DAIDS) will release the analysis report related to the Study Product and concurrently randomized placebo study arms prepared for DSMB review and associated data ("Phase II Analysis Report") to Company. The provision of the Phase II Analysis Report is not conditioned upon the graduation of the Study Product. Company agrees to restrict access of the Phase II Analysis Report to a named limited group of Company employees for the limited purposes of: 1) supporting Company's decision in moving forward with Phase III evaluation, if recommended by the DSMB and ACTIV; and 2) Study Product development. To protect the integrity of the ongoing Phase II study and of the Phase III study (if Phase III evaluation continues), if Company's Study Product graduates to Phase III, Company agrees to delay further release of information from the Phase II Analysis Report until completion of the Phase III Study and after NIAID (DAIDS), Investigators and Company jointly publish the results in a timely manner. Notwithstanding the above, if Company's Study Product does not graduate to Phase III, the Parties will collaborate to publish the results of the Phase II portion of the Study in a timely manner.

12. PUBLICATIONS AND PRESS RELEASES

12.1 Any publications based on the results of the Clinical Trial and originating from NIAID (DAIDS) or the Investigators will conform to the latest version of the ACTG Publications Standard Operating Procedure, incorporated herein as Addendum II. Unless requested otherwise by Company, NIAID (DAIDS) will acknowledge Company as the source of the Study Product in any NIAID (DAIDS) publication resulting from the Clinical Trial and will ensure that the Investigators do the same in their publications resulting from the Clinical Trial.

12.2 Recognizing that employees of either Party may play an important role in the design, analysis and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the generally accepted customs pertaining to authorship. NIAID (DAIDS) will ensure that the Investigators include appropriate individuals from both Parties in their publications resulting from the Clinical Trial.

12.3 Each Party will provide, and NIAID (DAIDS) will ensure that the Investigators provide, a copy of any abstract or manuscript to the other Party prior to submission for publication with sufficient time for review and comment, as outlined in the ACTG Publications Standard Operating Procedure [Manuscripts: ten (10) days; Abstracts: five (5) days]. The publication or other disclosure will be delayed for up to thirty (30) additional business

days for manuscripts and up to five (5) business days for abstracts, upon written request by either Party as necessary to preserve U.S. or foreign Patent or other intellectual property rights. At either Party's request during its period of review specified above, said Party's Confidential Information shall be removed from such publication or disclosure. Each Party agrees that, following the receiving Party's review of the manuscript and/or abstract for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish, present or use any Clinical Trial data.

12.4 Each Party will provide, and NIAID (DAIDS) will ensure that the Investigators provide, a copy of any proposed press release to the other Party for review at least five (5) business days in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish the press release.

13. CONFIDENTIAL INFORMATION

13.1 Either Party may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct the Clinical Trial. The disclosing Party will place a confidentiality notice on all the Confidential Information. The disclosing Party will reduce confidential non-written communications to writing within thirty (30) business days of first disclosure. Regarding oral disclosures of Confidential Information, if a Party does not reduce oral Confidential Information to writing, the Party must verbally provide notice of the confidential nature of the oral disclosure at the time it is disclosed for the oral Confidential Information to be considered confidential under this Agreement. Each Party receiving Confidential Information agrees that any information so designated will be used by it only for the purposes of the Clinical Trial. Any Party may object to the designation of information as Confidential by the other Party.

13.2 Unless expressly provided otherwise, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA), 5 U.S.C. § 552, or other applicable laws and/or regulations to disclose the Confidential Information, except that NIAID (DAIDS) and Company may disclose Confidential Information to those of their representatives, agents, officers, grantees, contractors, consultants, employees and potential Clinical Research Sites (collectively, "Agents") to the degree necessary to conduct the Clinical Trial. The Parties will ensure that their respective Agents maintain the confidentiality of Confidential Information in accordance with the terms of this Agreement.

13.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. Current NIH policy requires that a brief synopsis, the

enrollment status and study results for all NIH-funded clinical trials be posted in the ClinicalTrials.gov registry of clinical studies, available through the NIH website. NIAID (DAIDS) shall be responsible for submitting information to ClinicalTrials.gov after Company's prior review of information from the Study Product.

13.4 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given an opportunity to seek a court order to enjoin from disclosure.

13.5 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above, or five (5) years after the expiration or termination date of this Agreement. Either Party may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

14. INTELLECTUAL PROPERTY

14.1 Ownership of any invention made solely or jointly by NIAID (DAIDS), the Clinical Research Sites and Investigators, or other NIAID (DAIDS) contractors or grantees as a consequence of conducting the Clinical Trial and involving the Study Product, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party claims by virtue of this Agreement any right, title, or interest in or to any issued Patents or pending Patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by Company to NIAID (DAIDS) with respect to the Study Product, other than the limited right to use the Study Product for the performance of the Protocol in accordance with the terms of this Agreement.

14.2 **NIAID (DAIDS) Intellectual Property.**

14.2.1 The Government will retain title to any Patent or other intellectual property rights in inventions made by NIAID (DAIDS) employees in the course of the Clinical Trial.

14.2.2 NIAID (DAIDS) agrees to notify Company of any such Invention and is willing to disclose it to Company under an appropriate confidentiality Agreement. Company may apply for exclusive license rights to any patentable Invention made by NIAID (DAIDS) employees that might arise during the clinical research and the NIH will consider Company's application for a license consistent with 37 C.F.R. Part 404.

14.3 **Company Intellectual Property.** Company will retain title to any Patent or other intellectual property rights in Inventions made by its employees during the course of the Clinical Trial.

14.4 **Clinical Research Site/Investigator Intellectual Property.** This Agreement does not grant or preclude intellectual property rights, including, but not limited to, Inventions made by ACTG, the Investigators, or other NIAID (DAIDS) contractors or grantees during the course of the Clinical Trial. Company may enter into a separate agreement with the Clinical Research Sites or Investigators regarding intellectual property rights that do not interfere with the conduct of this Clinical Trial or contradict the terms of this Agreement.

14.5 **Joint NIAID (DAIDS)-Company Intellectual Property.** NIAID (DAIDS) and Company will have joint intellectual property rights in Inventions made jointly by their employees during the course of the Clinical Trial.

15. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

16. LIABILITY, INDEMNIFICATION AND INSURANCE

16.1 **Liability.** Activities carried out under this Agreement are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) as implemented under the amended declaration, "Public Readiness and Emergency Preparedness Act Coverage for medical countermeasures against COVID–19," issued on March 17, 2020 (85 Federal Register 15198). The PREP Act provides immunity from liability claims against manufacturers, distributors, program planners and other qualified persons ("Covered Persons") arising from the administration and use of covered countermeasures, as specified in a declaration by the Secretary of HHS ("Secretary") [See section 319F-3 of the Public Health Service Act (42 U.S.C. § 247d-6d)]. The exception to this immunity is acts of willful misconduct by the Covered Persons. The Study Product is considered a drug to treat, prevent or mitigate COVID-19, and as such is a covered countermeasure under the Secretary's declaration. Informed consent forms used in the Clinical Trial will include a sufficient description of the PREP Act for participants to understand that all Covered Persons have immunity from liability under the PREP Act, and what compensation may be available under the PREP Act Countermeasure Injury Compensation Program [See section 319F-4 of the Public Health Service Act (42 U.S.C. § 247d-6e)]. To the extent that PREP Act coverage is not available, each Party shall be liable for any loss, claim, damage or liability that it incurs as a result of its direct activities under this Agreement, except that NIAID (DAIDS), as an agency of the U.S. Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171.

16.2 **Indemnification.** NIAID (DAIDS) is prohibited under the Anti-Deficiency Act, 31 U.S.C. § 1341 from indemnifying Company for any losses incurred as a result of this Clinical Trial. Each Party will be liable for the losses, claims, damages or liabilities that it incurs as a result of its activities under this Agreement. Company's right and obligation to defend NIAID (DAIDS) and Company's control over the defense and settlement of any claim against NIAID (DAIDS) will be subject to the consent of NIAID (DAIDS) and the Department of Justice.

To the extent that PREP Act coverage is not available, Company will defend, indemnify and hold harmless NIAID (DAIDS)'s grantees and contractors and their respective agents and employees ["Indemnitee(s)"] from any and all liabilities, damages, losses, claims, action, suits and expenses, including attorneys' fees and court costs (collectively "Claims") to the extent caused by the administration or use of the Study Product during the course of the Clinical Trial, provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if each of the following conditions is met:

16.2.1 The Claim was not proximately caused by the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, any written instructions from Company, and this Agreement.

16.2.2 The Claim was not caused by the gross negligence, recklessness or willful misconduct of any Indemnitee, provided that any action properly taken by the Indemnitee in compliance with the Protocol or written instructions from Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if a Claim is jointly caused by the negligence of any Indemnitee and the administration or use of the Study Product, then Company will provide defense and indemnification to the extent the Claim was caused by the administration of the Study Product.

16.2.3 Company is promptly notified of the Claim, provided that the failure to give such notice will not abrogate or diminish Company's defense and indemnity obligation if Company has or receives knowledge of the existence of the Claim by any other means or if such failure does not prejudice Company's ability to defend the Claim.

16.2.4 Company will have sole control over the defense and settlement of the Claim(s) directed against Company.

16.2.5 Company will have the right to select defense counsel and to direct the defense and settlement of the Claim(s) directed against Company.

16.2.6 Company will provide a diligent defense against and/or settlement of any Claims for which defense and indemnification are provided under this Agreement whether such Claims are rightfully or wrongfully made. Company will have the right to settle such Claims, at Company's sole expense and in Company's sole

discretion. Indemnitee(s) will fully cooperate, at Company's expense, with Company and its legal representatives in the investigation and defense of any Claim for which defense and indemnification are provided under this Agreement.

16.2.7 The Indemnitee(s) will at all times have the right to fully participate in the defense of any Claim at their own expense and for their own account.

16.3 **Insurance.** Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the research related injury and indemnification obligations assumed under this Agreement. Upon request, Company will provide evidence of its insurance or self-insurance to NIAID (DAIDS).

17. DISPUTE RESOLUTION

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the dispute will be referred to the Director of **DAIDS,** NIAID (or his/her designee) and an appropriate authorized representative of Company for resolution. If the Director of DAIDS (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute through good faith negotiations within thirty (30) days, the dispute will be referred to the Director of **NIAID** (or his/her designee) and the authorized representative of Company. If the Director of NIAID (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute, either Party may pursue any and all administrative or judicial remedies that may be available.

18. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the other Party, enter into any contract, warranty or representation as to any matter. Neither Party will be bound by the acts of the other Party.

19. NON-ENDORSEMENT

By entering into this Agreement, NIAID (DAIDS) does not directly or indirectly endorse any product or service provided, or to be provided, by Company. Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However, Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

20. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

21. SURVIVABILITY

The provisions (Clinical Research Sites and Investigators), (Investigational New Drug Application Sponsorship), (Supply, Distribution and Use of Study Product), (Human Subjects Protection), (Data Collection, Analysis and Management), (Publications and Press Releases), (Confidential Information), (Intellectual Property), (Liability, Indemnification and Insurance), (Dispute Resolution), (Independent Contractors), (Non-Endorsement), (Amendments) and this Section (Survivability) will survive the expiration or earlier termination of this Agreement.

22. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement. The provisions of this Agreement are severable and, in the event that any provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

23. ASSIGNMENT

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without prior written notification to the other Party. The terms and conditions of this Agreement shall be binding on and inure to the benefit of the permitted successors and assigns of the Parties.

24. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

25. TERM AND TERMINATION

Unless terminated sooner in accordance with this Term and Termination Section, this Agreement will expire upon completion of the Clinical Trial. The Parties may terminate this Agreement at any time by mutual written consent. Either Party may unilaterally terminate this Agreement at any time by giving written notice at least thirty (30) days prior to the desired termination date. The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol, and Company will supply enough Study Product to

complete the Clinical Trial. In the event that Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution, Company must notify NIAID (DAIDS) within at least thirty (30) days of the dissolution.

26. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt) or via facsimile followed by confirmational hard copies sent via international courier when it is necessary to receive or deliver documents within a very short period of time [less than one (1) day].

For Company:

(b)(6) (b)(6)
(b)(6)@lilly.com
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

For regulatory matters:

(b)(6) (b)(6)
(b)(6)@lilly.com
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Safety Reports: Mailindata_gsmtindy@lilly.com

Annual Reports: GPSPeriodicReports@Lilly.com

For quality assurance matters:

(b)(6) Dir-QA-Materials/Analytical Distribution
(b)(6)@lilly.com
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

For technical matters:

(b)(6) (b)(6)
(b)(6)@lilly.com
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

For NIAID (DAIDS):

Peter S. Kim, M.D.

Director
Therapeutics Research Program
DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9E50
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @nih.gov

For regulatory matters:

Mary Anne Luzar, Ph.D., M.S.
Chief
Regulatory Affairs Branch
DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9B30
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

For clinical matters:

Arzhang Cyrus Javan, M.D., M.P.H., D.T.M.&H.
Medical Officer
DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9E40
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @nih.gov

27. COUNTERPARTS

This Agreement may be executed in counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument.

SIGNATURES BEGIN ON THE NEXT PAGE

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

Peter S. Kim -S Digitally signed by Peter S. Kim -S
Date: 2020.07.20 12:29:58 -04'00'

(Signature) (Date)

Peter S. Kim, M.D.
Director
Therapeutics Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health

(b)(6)

Digitally signed by (b)(6)
MBA
DN: cn=(b)(6) o=Eli Lilly and Company, ou=Trial Capabilities, email=(b)(6) @lilly.com, c=US
Date: 2020.07.20 14:18:42 -04'00'

20 July 2020

(Signature) (Date)

(b)(6)
(b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

(Signature) (Date)

(b)(6)
(b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

cc: Principal Investigators, Clinical Research Sites

(Signature) (Date)

(b)(6)

(b)(6)

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

(b)(6)

(Signature) 20 JUL 2020 (Date)

(b)(6)

(b)(6)

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

cc: Principal Investigators, Clinical Research Sites

DAIDS PROTOCOL REGISTRATION MANUAL

Office for Policy in Clinical Research Operations Division of AIDS

EFFECTIVE

DAIDS PROTOCOL REGISTRATION MANUAL

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DAIDS PROTOCOL REGISTRATION MANUAL i

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I. Introduction

The Division of AIDS (DAIDS) Office for Policy in Clinical Research Operations (OPCRO) has established a protocol registration manual that details, in a step-wise manner, the protocol registration process to ensure that all clinical research sites (CRSs) conducting National Institute of Allergy and Infectious Disease (NIAID)DAIDS-supported and/or -sponsored clinical research do so in accordance with DAIDS Clinical Research Policies and Standard Procedures in addition to all applicable regulations for human subjects protection and the use of investigational drugs, biologics and/or devices. Each CRS will complete the protocol registration process for all clinical research supported and/or sponsored by NIAID (DAIDS) that is reviewed by CSRC or PSRC. Submission of an incomplete package by failing to include all required documents for protocol registration at the time of submission to the DAIDS PRO will result in processing delays until all the required documents are received.

The DAIDS Protocol Registration Manual is a reference tool to help CRSs successfully complete the DAIDS protocol registration process. This manual explains the different types of protocol registration submissions as well as a list of the required documents for each type of submission. Critical pointers are provided in the NOTES throughout the DAIDS Protocol Registration Manual. Failure to include any required documents for protocol registration at the time of submission to the DAIDS PRO will result in processing delays until all the required documents are received.

The protocol registration process begins once a protocol has completed the DAIDS protocol development requirements. All protocols must receive final DAIDS approval either after DAIDS Clinical Sciences Review Committee (CSRC) or Prevention Sciences Review Committee (PSRC) and after regulatory review and DAIDS Medical Officer sign-off. For protocols conducted under a DAIDS-held Investigational New Drug (IND) Application, the final DAIDS approved version of the protocol must be submitted to the U.S. Food and Drug Administration (FDA).

The DAIDS protocol registration process verifies that CRSs have received the necessary Institutional Review Board (IRB)/Ethics Committee (EC) and other applicable Regulatory Entity (RE)/Regulatory Authority approvals and have provided to DAIDS all documentation pertaining to investigator qualifications and responsibilities that are required by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the U.S. federal regulations and the National Institutes of Health (NIH). The DAIDS protocol registration process also verifies that site-specific informed consent forms contain the necessary information to comply with ICH, and the U.S. federal regulations. This includes the basic and additional informed consent form elements as required by U.S. federal regulations at 45 CFR 46.116 and 21 CFR 50.25.

II. Summary of Changes

This manual has been reviewed for accuracy and updated to meet 508 compliance guidelines. Several sections have been updated to be consistent with current NIAID (DAIDS) requirements. Key changes to note in this version of the Manual include:

1. DAIDS requirement of Protocol Signature Page (PSP) to document the commitment of the Investigator of Record (IOR) to conduct the trial in compliance with regulations/Laws and ensure compliance with ICH E6 GCP 4.5.1 and 5.6.3.

2. The requirement to submit the Clinical Trial Application (CTA) Form/documentation that identifies the study sponsor.

3. The requirement to submit translation certificate (or translation documentation) confirming a true and accurate translation of documents from local language into English language.

4. Clarification regarding staff that must be listed on the Form FDA 1572 an/or DAIDS IOR Forms in compliance with U.S. regulations and ICH E6 standards.

5. Adjusted the timeline to submit updated DAIDS IOR Forms and Form FDA 1572s from 30 days to 15 days.

6. Formatting changes and hyperlinks added to improve navigation of the manual.

7. Clarified requirements regarding documents required to be submitted to DAIDS from IRBs, ECs, REs, and Regulatory Authorities.

8. Provide guidance on the use of electronic signatures.

9. Change to requirements regarding justifications for non-submission of Regulatory Authority approvals of full version protocol Amendments and Letter of Amendments (LOA).

10. Clarification of Continuing Review requirements based on the October 2018 FDA guidance, 21 CFR 56.109 and 45 CFR 46.109.

This Manual supersedes the version 3.0 dated April 2015.

III. Protocol Registration Required Documents by Submission Type

DAIDS reviews and approves the latest version of each protocol and Sample Informed Consent Form (ICF) before distribution to the CRSs. CRSs are required to submit the initial version and all subsequent versions of a NIAID (DAIDS) -supported and/or -sponsored protocol, including the DAIDS-approved Sample ICF and site-specific ICFs, to their reviewing IRB/EC and other applicable RE/Regulatory Authority(ies) for review and approval.

Prior to implementing the protocol and enrolling participants, a CRS must receive approval from their IRB/EC and other applicable RE/ Regulatory Authorities. In addition, the CRS must successfully complete the DAIDS protocol registration process. When cleared to open to enrollment, a CRS will be notified by the appropriate DAIDS scientific program (e.g., Program/Contracting Officer Representative), Operations Center or Data Management Center when enrollment may begin.

Detailed information on specific requirements for each required document for protocol registration is included in sub-sections A-H of Document Requirements (Concise) of the manual.

A. Submission Requirements by Submission Type

Submission Type	Submission Requirements	Document Requirement	Page
Initial Registration	Form FDA 1572 for IND studies and DAIDS IOR Form for Non-IND studies	Form FDA 1572/DAIDS IOR Form	10
	IOR CV	Curriculum Vitae	11
	IOR Medical License (License equivalent)	Medical License	12
	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submissions Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Documentation of Pediatric risk/benefit category per 45 CFR 46 and 21 CFR 50 (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Clinical Trial Application Form/document	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Regulatory Entity (RE)/Regulatory Authority Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority/Acknowledgement Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All RE/Regulatory Authority Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IBC Approval Letter and applicable correspondence (when applicable)	Institutional Biosafety Committee (IBC)	13
	Protocol Signature Page	Protocol Signature Page (PSP)	14

Submission Type	Submission Requirements	Document Requirement	Page
	Site Specific Informed Consent(s) - all applicable languages. All ICFs required by the protocol are required to be submitted or justification for the omission is required.	Site Specific Informed Consents	15
	Site Specific Informed Assent(s) - all applicable languages	Site Specific Informed Consents	15
	Translation Certificate (if applicable)	Translation requirements	36
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Amendment	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Documentation of Pediatric risk/benefit category per 45 CFR 46 and 21 CFR 50 (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Approval/Acknowledgement Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All RE/Regulatory Authority Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Protocol Signature Page	Protocol Signature Page (PSP)	14
	Site Specific ICF - all applicable languages. All previously approved ICFs must be submitted or justification provided for their omission must be provided. Any new ICFs added within the protocol ICFs must be submitted as an Additional ICF type or justification provided for their omission must be provided.	Site Specific Informed Consents	15

Submission Type	Submission Requirements	Document Requirement	Page
	Site Specific Informed Assent(s) - all applicable languages. All previously approved Assents must be submitted, or justification provided for their omission must be provided. Any new Assents required must be submitted as Additional ICF types or justification provided for their omission must be provided.	Site Specific Informed Consents	15
	Translation Certificate (if applicable)	Translation requirements	36
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Letter of Amendment (LOA)	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submissions Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Documentation of Pediatric risk/benefit category per 45 CFR 46 and 21 CFR 50 (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Approval/Acknowledgement Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Site Specific ICFs - all applicable languages. Any revised ICFs should be submitted as a Site Revised ICF submission along with the LOA. Any new ICFs added within the protocol ICFs must be submitted as an Additional ICF type or justification provided for their omission must be provided.	Site Specific Informed Consents	15

Submission Type	Submission Requirements	Document Requirement	Page
	Site Specific Informed Assent(s) - all applicable languages. Any revised Assent forms should be submitted as a Site Revised ICF submission along with the LOA. Any new Assents required must be submitted as Additional ICF types or justification provided for their omission must be provided.	Site Specific Informed Consents	15
	Protocol Signature Page	Protocol Signature Page (PSP)	14
	Translation Certificate (if applicable)	Translation requirements	36
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Administrative Registration	Form FDA 1572 for IND studies and Form FDA 1572 or IOR Form for Non-IND studies	Form FDA 1572/DAIDS IOR Form	10
	IOR CV	Curriculum Vitae	11
	IOR Medical License (License equivalent)	Medical License	12
	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submissions Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
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	All RE/Regulatory Authority Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IBC Approval Letter and applicable correspondence (when applicable)	Institutional Biosafety Committee (IBC)	13
	Protocol Signature Page	Protocol Signature Page (PSP)	14
	Translation Certificate (if applicable)	Translation requirements	36

Submission Type	Submission Requirements	Document Requirement	Page
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Change of Investigator	Form FDA 1572 for IND studies and Form FDA 1572 or IOR Form for Non-IND studies	Form FDA 1572/DAIDS IOR Form	10
	IOR CV	Curriculum Vitae	11
	IOR Medical License (License equivalent)	Medical License	12
	Protocol Signature Page	Protocol Signature Page (PSP)	14
Continuing Review	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
Site Initiated Revised ICFs	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
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	RE/Regulatory Authority Approval/Acknowledgement Letters (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Site Specific ICFs - all applicable languages	Site Specific Informed Consents	15
	Site Specific Informed Assent(s) - all applicable languages	Site Specific Informed Consents	15
	Translation Certificate (if applicable)	Translation requirements	36

Submission Type	Submission Requirements	Document Requirement	Page
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Updated Form FDA 1572 or DAIDS IOR Form	Form FDA 1572 for IND studies and Form FDA 1572 or IOR Form for Non-IND studies	Form FDA 1572/DAIDS IOR Form	10
Deregistration	Request stating that the CRS no longer intends to participate in the protocol(s) and/or A Copy of the IRB/EC closure/termination letter for the protocol if the protocol has been closed with the IRB/EC at the time of deregistration	Deregistration	57
Suspension or Termination of IRB/EC Approval	Documentation from the IRB/EC that identifies the reason for suspension or termination	Suspension or Termination of IRB/EC Approval	31

IV. Document Requirements (Concise)

A. Form FDA 1572/DAIDS IOR Form

Section	General Requirement	Detailed Requirement
Section 1 - Name and Address of Investigator of Record (IOR)	Complete legal name (first and last name) and address of the IOR at the CRS that is responsible for the conduct of the clinical trial. The complete legal name of the IOR and the IOR's complete office address (complete physical location/street address/country)	Section 1 - Name and Address of Investigator of Record (IOR)
Section 2 - Education, Training, and Experience	Requires the IOR to check the appropriate box on how they plan to verify their education, training and experience that qualifies them as an expert in the clinical investigation of the study product (drug or biologic) being tested	Section 2 - Education, Training, and Experience
Section 3 - Name and Address of Location(s) Where the Study Will be conducted	Complete name and address of all locations where the clinical trial will be conducted and where clinical data will be generated or collected. The complete name and physical address of all the locations (medical school, hospital, clinics, additional locations, or research facility)	Section 3 - Name and Address of Location(s) where the Study will be conducted
Section 4 - Name and Address of Clinical Laboratory	Complete name(s) and complete physical address (including country) of ALL clinical laboratories or testing facilities which will be used for the clinical trial to process study related and/or study defined samples that will directly contribute to or support the clinical trial	Section 4 - Name and Address of Clinical Laboratory
Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/ Regulatory Authority(ies)) and Institutional Biosafety Committees (IBCs)	Complete name and address of all IRBs, ECs and other applicable Regulatory Authority(ies) and IBCs which are responsible for the review and approval for the conduct of clinical trials at a CRS	Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/Regulatory Authority(ies) and Institutional Biosafety Committees (IBCs)
Section 6 - Names of Sub-Investigators	Complete legal name (first and last name) of study staff at a CRS responsible for making a "direct and significant contribution to data"	Section 6 - Names of Sub-Investigators
Section 7 - Protocol Name and Protocol Number	DAIDS ES/Network protocol ID number and the complete protocol title	Section 7 - Protocol Name and Protocol Number
Section 8 - Clinical Protocol Information	Leave blank	Section 8 - Clinical Protocol Information
Sections 9 - Commitments	Read and understand	Sections 9, 10 and 11

Section	General Requirement	Detailed Requirement
Section 10 - Date	Handwritten or electronic date is acceptable. If utilizing electronic date, an electronic signature must be utilized, and the electronic date and the date identified in the electronic signature must correspond. See Signature Requirement Guidance regarding electronic signature requirements.	Sections 9, 10 and 11
Section 11 - Signature of Investigator	Handwritten or electronic signature is acceptable. If utilizing electronic signature, an electronic date must be utilized and the electronic date and the date identified in the electronic signature must correspond See Signature Requirement Guidance regarding electronic signature requirements.	Sections 9, 10 and 11

B. Curriculum Vitae

	General Requirement	Detailed Requirement
Curriculum Vitae (CV)	Submitted (or on file and less than two years old)	Curriculum Vitae (CV)
	Name on the CV matches IOR identified on current Form FDA 1572 or DAIDS IOR Form	
	Complete (all pages submitted, and the document is legible)	
	Dated: Handwritten or electronic date is acceptable. If utilizing electronic date, an electronic signature must be utilized, and the electronic date and the date identified in the electronic signature must correspond. See Signature Requirement Guidance regarding electronic signature requirements.	
	Signed: Handwritten or electronic signature is acceptable. If utilizing electronic signature, an electronic date must be utilized and the electronic date and the date identified in the electronic signature must correspond See Signature Requirement Guidance regarding electronic signature requirements.	

C. Medical License

	Review Requirement	Detailed Requirements
Medical License (ML)	Name on the ML or equivalent document matches IOR identified on current Form FDA 1572 or IOR Form	Curriculum Vitae (CV) and Medical License
	The ML or equivalent document is current (not expired). Note that if the ML does not designate an expiration date, it can be accepted.	

D. IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation

	Review Requirement	Detailed Requirements
IRB/EC/RE/Regulatory Authority(ies)	Complete protocol title or short title for the current DAIDS approved version of the protocol.	IRB/EC Approvals
	DAIDS-ES and/or Network Protocol ID	
	DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS and/or the final version date of the protocol document	Regulatory Entity (RE)/Regulatory Authority Approvals
	Final approval letter (conditional approvals not accepted)	
	Pediatric Risk Assessment included in the IRB approval Letter, if applicable	Documentation of Pediatric Risk/Benefit Category
	For LOAs and full version protocol amendments - The date that the amended protocol documents were submitted to the reviewing IRB/EC must be identifiable or provided on the IRB/EC approval letter or on the memo/CRS note, and the date must predate the final IRB/EC approval	Amendment Registrations
		Letter of Amendment (LOA) Registration
	Approval letters from all applicable IRB/EC/ RE/Regulatory Authority(ies) as listed on the Form FDA 1572 or DAIDS IOR Form or justification for their omission	Amendment Registrations
		Letter of Amendment (LOA) Registration

E. Institutional Biosafety Committee (IBC)

	Review Requirement	Detailed Requirements
Institutional Biosafety Committee (IBC)	Complete protocol title or short title for the current DAIDS approved version of the protocol	Institutional Biosafety Committee (IBC) Approval
	DAIDS-ES and/or Network Protocol ID	
	DAIDS Protocol Version Number from the final version of the protocol as approved by DAIDS and/or the final version date of the protocol document	
	Final approval letter (conditional approvals not accepted)	

F. Protocol Signature Page (PSP)

	Review Requirement	Detailed Requirements
Protocol Signature Page (PSP)	Submitted for Initial, Amendment or LOA and Change of IOR submissions Contains the following statement verbatim, "I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies."	Protocol Signature Page (PSP)
	Signed by the IOR (s) that is listed on item #1 on the site's current Form FDA 1572/DAIDS IOR Form on file at DAIDS. Handwritten or electronic signature is acceptable. If utilizing electronic signature, an electronic date must be utilized, and the electronic date and the date identified in the electronic signature must correspond. See Signature Requirement Guidance regarding electronic signature requirements.	
	Dated: Handwritten or electronic date is acceptable. If utilizing electronic date, an electronic signature must be utilized, and the electronic date and the date identified in the electronic signature must correspond. See Signature Requirement Guidance regarding electronic signature requirements.	
	Lists the complete DAIDS Protocol Title	
	Lists the DAIDS Protocol Number	
	Lists the correct DAIDS Protocol Version (include the protocol and LOA version when applicable)	
	Lists the correct DAIDS Protocol Version Date	

G. Site Specific Informed Consents

	Review Requirement	Detailed Requirements
Site Specific Informed Consent/ Assent Forms	Lists the complete DAIDS Protocol Title	Site-Specific Informed Consent Forms (ICFs)
	Lists the DAIDS Protocol Number	
	Lists the correct DAIDS Protocol Version	
	All ICFs included in the DAIDS approved protocol are submitted or justification for their omission is provided	
	All ICFs are submitted in all applicable languages or justification for their omission is provided	
	All ICFs should meet all requirements as specified in CFR 46.116, 21 CFR 50.25 DAIDS Policy DWD-POL-CL-02.00 and local laws and regulations	
	Full version protocol Amendments only - All ICFs Types previously registered as part of initial registration are submitted or justification for their omission is provided	

H. Clinical Trial Applications Form/Document

	Review Requirement	Detailed Requirements
Clinical Trial Application Form/Document	Lists the complete DAIDS Protocol Title	Clinical Trial Applications (CTA) for In-country Regulatory Entity (RE)/Regulatory Authority(ies)
	Lists the DAIDS Protocol Number	
	Lists the correct DAIDS Protocol Version	
	Lists the correct DAIDS Protocol Version dated	
	Documentation to confirm that the correct sponsor is identified	
	Complete (all pages) and legible	

V. Protocol Registration Required Documents (Detailed)

A. Form FDA 1572/DAIDS IOR Form

REQUIRED FOR:

- INITIAL REGISTRATION
- WHEN THERE IS ANY MAJOR CHANGE TO THE INFORMATION ON THE CURRENT FORM FDA 1572/DAIDS IOR FORM.

Form FDA 1572 must be submitted for studies being conducted under an IND application. The DAIDS IOR Form or Form FDA 1572 can be submitted for an initial registration for studies not conducted under an IND application.

A signed Form FDA 1572/DAIDS IOR Form is required for each investigator that participates in any clinical trial (drug or biologic). By signing the Form FDA 1572/DAIDS IOR Form, the Investigator of Record (IOR) affirms that he/she will conduct the clinical trial according to the research protocol and all applicable U.S. federal regulations and the ICH E6 GCP guidelines. By signing the Form FDA 1572/DAIDS IOR Form, investigators at non-U.S. sites affirm to DAIDS their commitment to comply with local laws and regulations throughout the course of the clinical trial.

All CRSs participating in a NIAID (DAIDS)-supported and/or -sponsored clinical trials conducted under an IND must submit a copy of the signed and dated Form FDA 1572 to the DAIDS PRO as part of the protocol registration submission for review and for submission to the U.S. FDA.

NOTE: *CRSs are required to retain the original signed Form FDA 1572/DAIDS IOR Form in their regulatory files at the site. Original Forms should not be sent to the DAIDS PRO.*

CRSs requiring more space than what is provided on the Form FDA 1572/DAIDS IOR Form can use a supplemental page. The supplemental page provides additional space to document: additional research locations and addresses; laboratory facilities and addresses; and the names of additional sub-investigators. The supplemental page should identify the CRS and protocol number. If used, a copy of the supplemental page must also be sent to the DAIDS PRO as part of the protocol registration submission.

A CRS must update and submit within 15 calendar days a revised copy of the Form FDA 1572/DAIDS IOR Form when there is ANY major change to the information on the current Form FDA1572/DAIDS IOR Form submitted to the DAIDS PRO. Any correction or revision requires the IOR to sign and date the newly revised form. CRSs must submit BOTH pages of the revised Form FDA 1572/DAIDS IOR Form to the DAIDS PRO even if the changes only affect one page of the form. An updated Form FDA 1572/DAIDS IOR Form that has the same date as the original or previous version will not be accepted.

NOTE: *Examples of major changes to the Form FDA 1572/DAIDS IOR Form include but are not limited to:*

- *Change in IOR*
- *Change in Sub-IOR*
- *Addition of a new or additional DAIDS approved location where the research will be conducted*
- *Addition of a laboratory*
- *Addition or change in an IRB/EC/ RE/Regulatory Authority(ies) that is responsible for review and approval of the clinical research protocol*

The most current version of the Form FDA 1572/DAIDS IOR Form is available for download on the DAIDS RSC Website under the "Protocol Registration" section or from the U.S. FDA website.

B. How to complete the Form FDA 1572/DAIDS IOR Form

Below is detailed information to assist a CRS when completing these Forms.

1. Section 1 - Name and Address of Investigator of Record (IOR)

This section must contain the complete legal name (first and last name) and complete office address (complete physical location/street address) address of the IOR at the CRS that is responsible for the conduct of the clinical trial. Non-U.S. CRSs should include the complete physical address, including
the country.

If a CRS has more than one IOR sharing responsibilities for a clinical trial, the CRS has the following options:

- The CRS can submit a separate Form FDA 1572/DAIDS IOR Form for each IOR that is responsible for the study at that CRS(s) and other DAIDS approved location(s). The CRS must provide documentation explaining that the investigators listed on the two Form FDA 1572s/DAIDS IOR Forms are sharing responsibilities for the conduct of the study at the CRS and DAIDS approved additional location(s).
- The CRS can submit one Form FDA 1572/DAIDS IOR Form that lists both investigators in Section 1 of the Form FDA 1572. This indicates that both

investigators are sharing equal responsibilities for the conduct of the study at the CRS(s) and other DAIDS approved location(s). Each investigator must date sections 10 and sign Section 11 of the Form FDA 1572/DAIDS IOR Form.
The CRS must provide documentation stating that the two investigators listed on the Form FDA 1572 are sharing responsibilities for the conduct of the study at the CRS(s) and other DAIDS approved location(s).

NOTE: *Requirements for the documentation regarding shared responsibilities can be fulfilled in one of the following ways:*

- *Provide a written document that specifies how responsibilities will be shared and the role of each IOR at their respective location(s).*

- *Provide a copy of the study specific Delegation of Duties/Delegation of Responsibility log that indicates how responsibilities will be shared and the roles of each IOR at their respective location(s).*

- *Provide a statement in item 1 of the Form FDA 1572/DAIDS IOR Form that specifies that the two IORs are Co-Investigators and how responsibilities will be shared and the role of each IOR at their respective location(s).*

2. Section 2 - Education, Training, and Experience

This section requires the IOR to check the appropriate box on how they plan to document their education, training and experience that qualifies them as an expert in the clinical investigation of the study product (drug or biologic) being tested. The box marked "Curriculum Vitae" should be checked and a copy of the IOR's CV must be included in the registration packet that is submitted to the DAIDS PRO. DAIDS does not require the submission of CVs for sub-investigators. However, sites should keep a copy of all sub-investigator CVs in the regulatory files at the site. DAIDS requires that all CVs be submitted in English and must be signed and dated.

3. Section 3 - Name and Address of Location(s) where the Study will be conducted

This section must list the complete name and physical address of all locations (medical school, hospital, clinics, satellite sites, or research facility) where the clinical trial will be conducted and where clinical data will be generated or collected. This includes facilities where participants will be seen and study procedures performed. Non-U.S. CRSs should include the country in addition to the complete physical address.

If a CRS utilizes a DAIDS-approved pharmacy, it is not necessary to list the pharmacy on the Form FDA 1572/DAIDS IOR Form. If a CRS out-sources the pharmacy responsibilities

for a clinical trial the CRS must list the name and complete physical address of the contracted pharmacy in Section 3.

If an IOR is conducting the same research protocol at more than one CRS overseen by the same IRB/EC, then it is acceptable to submit one Form FDA 1572/DAIDS IOR Form which lists all locations where the clinical trial will be conducted. If more than one CRS is included in Item 3, include the DAIDS site ID (if available) for each CRS.

4. Section 4 - Name and Address of Clinical Laboratory

This section must list the complete name(s) and complete physical address of ALL clinical laboratories or testing facilities which will be used for the clinical trial to process study related and/or study defined samples that will directly contribute to or support the clinical trial (e.g., diagnostic labs performing blood work, imaging centers, cardiology labs, non-local labs). This may include analytical labs that provide pharmacokinetic analysis, and laboratories supplying efficacy data. The official name of the laboratory (e.g., Department of Pathology) should be included. If multiple CRSs and/or locations are listed on the Form FDA 1572/DAIDS IOR Form, the corresponding clinical laboratories must be listed for each CRS and/or location.

Exceptions for not including ALL clinical laboratories or testing facilities include:

- If a primary laboratory is sending samples to a satellite or other contract labs for additional testing, or
- If a laboratory is being used only to store study samples.

The additional labs do not need to be listed as long as the primary laboratory can trace, through written records, the shipment of samples to the additional labs where the tests were performed.

5. Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/Regulatory Authority(ies) and Institutional Biosafety Committees (IBCs)

This section must list the complete name and address of all IRBs, ECs REs, IBCs and all other Approving Entities including all National Regulatory Authorities which are responsible for the review and approval of clinical trials at a CRS prior to the CRS's initiation of the protocol and during the implementation of the study (if applicable).

NOTE: *In addition to U.S. FDA requirements, DAIDS requires that all sites participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials list all authorities that must review /approve/acknowledge the clinical trial prior to implementation at a CRS.*

These regulatory entities may include any authorities that regulate, provide permits and/or provide authorization before commencing any clinical trial at a CRS.

The official name (refer to the title provided on the IRB/EC and all other RE/Regulatory Authority(ies) approval letter(s)) and complete physical address of the IRBs/ECs and other REs/Regulatory Authority(ies) which reviewed the protocol should be included in Section 5. IRBs/ECs reviewing and approving the clinical trial do not have to be at the same location as the research being conducted.

NOTE: *The DAIDS PRO must receive an approval letter for each entity listed in Section 5 of the Form FDA 1572/DAIDS IOR Form. The RE/* Regulatory Authority *should not be removed/omitted from FORM FDA 1572/DAIDS IOR Form if they are not responsible for/or do not require the review and approval of full version protocol amendments, LOAs or changes to the CRS's site-specific ICF(s). The CRS Leader or IOR must document in writing to the DAIDS PRO and must also provide documentation (letter from the entity or SOP/guidance/regulation/procedure document of the entity) that shows that the entity doesn't review/approve full version protocol amendments/LOAs/Site specific ICs, when submitting registration materials.*

6. Section 6 - Names of Sub-Investigators

This section must list the complete legal name (first and last name) of all study staff at a CRS that are responsible for making a "direct and significant contribution to the data". A direct and significant contribution includes any persons directly responsible for the treatment or evaluation of research participants. This includes site personnel who have more than minimal involvement with the conduct of the research (performing study evaluations or procedures, conducting Informed Consent or providing intervention) or more than minimal study conduct-related contact with study participants or confidential study data, records, or specimens. A study specific Delegation of Duties/Delegation of Responsibilities log must be maintained at the site and should include all persons identified as providing a direct and significant contribution to the data.

Hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care and who do not make a direct and significant contribution to the data do not need to be listed. It is not necessary to include in Section 6 a person with only an occasional role in the conduct of the research (i.e., an on-call physician who temporarily dealt with a possible adverse event or a temporary substitute for any research staff). If a number of residents on rotation will participate in the clinical trial, a general statement regarding their planned participation may be included in Section 6.

The decision about whether to list a pharmacist or research coordinator on the Form FDA 1572/DAIDS IOR Form is the responsibility of the IOR at the CRS and should be based on the contribution that the individual makes to the study.

For example, a research pharmacist may prepare test articles and maintain drug accountability for many clinical trials that are ongoing concurrently at an institution. Because the pharmacist is not making a direct and significant contribution to the data for a particular study, it would not be necessary to list the pharmacist as a sub- investigator in Section 6, but he/she should be listed in the investigator's study records.

CRSs are required to list, at a minimum, a qualified sub-investigator (who will be responsible for fulfilling the requirements of the IOR should the IOR not be able to meet his/her requirement for any given reason). The complete legal name(s) of the sub-investigators who will assist the IOR in the conduct of the protocol should be listed in Section 6.

The IOR is responsible for determining the sub-investigators to be included on the Form FDA 1572/DAIDS IOR Form. Individuals who will sign study medication prescriptions and physicians who submit SAE/EAEs to DAIDS must be listed on the Form FDA 1572/DAIDS IOR Form. The IOR must designate a physician as a sub-investigator who will be responsible to serve as the IOR's backup.

NOTE: *Any physician who is responsible for the review and submission of SAE/EAEs to DAIDS must be listed in Section 6 of the Form FDA 1572/DAIDS IOR Form. Safety reports cannot be submitted by a physician who is not listed in Section 6 of the Form FDA 1572/DAIDS IOR Form.*

NOTE: *CRSs must list the CRS Leader as a Sub-investigator in Section 6 on all Form FDA 1572s /DAIDS IOR Forms if the IOR for the protocol, listed in Section 1, is not the CRS Leader. If the CRS Leader is the same person listed in Section 1 on the Form FDA 1572/DAIDS IOR Form, then the CRS Leader does NOT need to be listed again as a sub-investigator.*

NOTE: *Personnel at facilities where the study uses certain tests (e.g. cardiologist reading ECG or personnel at ECG facilities) do not have to be listed if they are not considered to be engaged in research activities. Per B1 of* OHRP's guidance document on engagement*; not all personnel are considered engaged in research activities unless they have other activities, such as administering study interventions being tested or evaluated or being a collaborator on the publication.*

7. Section 7 - Protocol Name and Protocol Number

The DAIDS ES/Network protocol ID number and the complete protocol title must be included in Section 7. CRSs should not include the DAIDS protocol version number, and/or protocol date in Section 7.

NOTE: *Short titles cannot be accepted and will result in the CRS having to submit a revised Form FDA 1572/ DAIDS IOR Form which will delay protocol registration.*

8. Section 8 - Clinical Protocol Information

NOTE: *The DAIDS IOR Form does not include a Clinical Protocol Information Section*

As the IND sponsor, DAIDS submits the protocol and all relevant information to the FDA on behalf of the investigator. This section should be left blank for both boxes. If DAIDS is not the IND sponsor for a trial, the IND sponsor is responsible for submitting the protocol and all relevant information including the Form FDA 1572 to the FDA and can determine the appropriate information for this section.

9. Sections 9, 10 and 11

NOTE: *These sections are numbered 8, 9, and 10 on the DAIDS IOR Form.*

The IOR must read Section 9, date Section 10 and sign Section 11. The complete legal handwritten or electronic signature of the IOR should be included in Section 11 and should correspond with the name in Section 1 of the Form FDA 1572/DAIDS IOR Form.

NOTE: *If more than one IOR is listed in Section 1 of the Form FDA 1572/ DAIDS IOR Form, both IOR's must sign and date this section.*

NOTE: *Electronic Signature are permissible using the Adobe Acrobat Self-Sign plug-in to insert your signature on fillable FDA forms. Security certificates associated with your digital signatures should be maintained at the site in compliance with 21 CFR 11.1(a). See Signature Requirement Guidance for additional information regarding electronic signatures. If utilizing electronic signatures, the date listed in the date field should be the same date identified on the electronic signature. If signed using hand written signature, the date must also be handwritten.*

NOTE: *If a CRS updates their Form FDA 1572/DAIDS IOR Form, the IOR(s) is responsible for signing and dating the new document even if the change(s) only affect page 1.*

NOTE: *An updated Form FDA 1572/ DAIDS IOR Form that is dated the same as the original or previous version will not be accepted.*

C. Financial Disclosure (FD) by Clinical Investigators

Effective July 1, 2014, any investigator (including sub-investigators) listed on the Form FDA 1572 must complete a financial disclosure (FD) form/statement for all DAIDS sponsored and/or supported studies where DAIDS holds the IND.

Per the regulatory requirements of 21 CFR 54, a person listed as an investigator or sub-investigator on the Form FDA 1572 must complete and submit financial disclosure information for all DAIDS sponsored and/or supported studies where DAIDS holds the IND. Each clinical trial Leadership and Operations Center has developed a generic financial disclosure form/statement for all network studies that are conducted under DAIDS held IND. These forms should be used unless DAIDS or the protocol team provides sites with a different FD Form/statement.

For all Non-Network studies that are conducted under a DAIDS held IND, DAIDS has developed a financial disclosure form/statement and this form is available on the DAIDS RSC website Financial Disclosure Form for Non-Network under Clinical Research Sites.

All original, completed and signed DAIDS approved network financial disclosure Forms/statements or the drug company-specific financial disclosure forms/statements must be filed and retained in a CRS's regulatory binder along with the original and/or updated, signed Form FDA 1572 for that study. These forms need not be submitted to DAIDS or the Network Operations Centers unless requested. For Non-DAIDS held INDs, investigators should follow the IND sponsor's instructions for the collection of financial disclosure form/statement (which may be a company or institution).

If FD forms/statements are required for a regulatory submission, CRS Leaders are responsible for making sure that a financial disclosure form is completed and submitted to their appropriate Network Operations Center per affiliated network requirements for each individual listed in Sections 1 and 6 of the Form FDA 1572.

This process is not required for Non-IND/IDE studies. Refer to the Protocol Registration Frequently Asked Questions on the DAIDS RSC website for additional information on the completion, implementation and collection of FD forms/statements.

D. Curriculum Vitae (CV) and Medical License (ML)

REQUIRED FOR:

- INITIAL REGISTRATION
- WHEN THERE IS ANY MAKOR CHANGE TO THE CURRENT CV ON FILE WITH THE DAIDS PRO.

OR

- UPDATED EVERY TWO YEARS

The IOR overseeing DAIDS-supported and/or sponsored clinical research must provide evidence of qualifications (experience, training and education) to assume responsibility for the conduct of a clinical trial. All CVs must provide sufficient documentation for DAIDS to verify the IOR's qualification to conduct a clinical trial.

IORs must sign and date their CV prior to submission to the DAIDS PRO. All IORs are required to submit an updated, newly signed and dated CV when there is ANY major change to the current CV on file with the DAIDS PRO or at a minimum of every 2 years.

If the IOR is a physician, a copy of the IOR's current medical license documentation or equivalent (i.e., documentation of good standing in the country where they are practicing) must be submitted with all CVs.

NOTE: *Examples of major changes to the IOR CV include but are not limited to:*

- *Change in contact information*
- *Change in education, Change in experience, New trainings*
- *New publications*

U.S. federal regulations require that the IOR's CV be submitted to the U.S. FDA for all studies being conducted under an IND. DAIDS, as the IND sponsor, submits the IOR CV to the U.S. FDA. Sub-investigators are not required to submit CVs to the DAIDS PRO. However, sites should keep a copy of all sub- investigator CVs in the regulatory files at the site.

DAIDS accepts a NIH Bio-Sketch formatted CV that includes education/training, current employment, past relevant employment, licensures/memberships, and any relevant publications.

The NIH Bio-Sketch formatted CV template is available at NIH Grant Application Guide.

NOTE: *Electronic Signature are permissible using the Adobe Acrobat Self-Sign plug-in to insert your signature on fillable FDA forms. Security certificates associated with your digital signatures should be maintained at the site in compliance with 21 CFR 11.1 (See Signature Requirement Guidance for additional information regarding electronic signatures.*

NOTE: *If handwritten signatures are used, the date must also be handwritten.*

E. Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals

REQUIRED FOR:

- ALL INITIAL, AMENDMENT and LOA REGISTRATIONS, ADMINSTRATIVE REGISTRATIONS
- CONTINUING/ ANNUAL REVIEW SUBMISSIONS
- SITE INITIATED REVISIONS TO SITE- SPECIFIC ICFs and SUBMISSION OF REVISED SITE ICF(s) IN RESPONSE TO A DISAPPROVAL NOTIFICATION.

1. IRB/EC Approvals

CRSs are required to submit to their IRB/EC, the initial version and all subsequent full version amendment and LOA versions of NIAID (DAIDS)-supported and/or sponsored clinical trials and observational studies for review and approval, including the DAIDS-approved sample ICF and site- specific ICFs to the DAIDS PRO. The site's submission to the IRB/EC should include DAIDS approved sample protocol and Site ICF, all site specific ICFs, and any material/information that the site plans to provide to participants. CRSs must submit to the DAIDS PRO a copy of ALL documentation to and from the IRB/EC along with a copy of all the final approval letter(s). Original documents should be kept in the regulatory files at the CRS. The IRB/EC approval letter(s) for all initial, full version protocol amendment, and LOA registrations must be a final approval not noting any required modifications or stipulations.

NOTE: *Documentation to and from IRB/EC includes but is not limited to:*

- *the submission letter from the site to the IRB/EC*
- *the letter(s) from the IRB/EC documenting queries and changes required to the site-specific ICFs*
- *site response to the queries*
- *final approval letter(s)*

All IRB/EC approval letter(s) must be able to be linked to the DAIDS-approved version of the protocol. If an IRB/EC approval letter(s) does not include the DAIDS required identifying information in their approval letters, CRSs can submit a memo with their IRB/EC submission that includes: identifying information corresponding to the protocol, lists all the documents submitted for IRB/EC review, as well as the date of submission to the IRB/EC. The required identifying information are:

- Complete Protocol Title as listed on the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both in the DAIDS SAMPLE ICF.

- DAIDS ES and/or Network Protocol ID Number.

- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS and/or the final version date of the protocol document approved by DAIDS.

The CRS's memo/submission letter can be used to document that the IRB/EC/RE/Regulatory Authority received the correct version of the protocol and may be included with the IRB/EC/RE/Regulatory Authority approval letters that are submitted to the DAIDS PRO.

NOTE: *The CRS's memo to the IRB/EC/RE/Regulatory Authority requesting review must pre-date the date on the final IRB/EC/RE/Regulatory Authority approval letter(s).*

NOTE: *Sites are strongly advised to document the date the CRS receives each final IRB/EC/RE/Regulatory Authority approval letter to ensure compliance with the DAIDS protocol registration policy regarding submission of amendment and LOA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final IRB/EC/RE approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.*

NOTE: *If the reviewing IRB transferred the responsibility to another IRB, a site needs to provide documentation of the delegation of authority to the other IRB to the DAIDS PRO*

NOTE: *If any of the IRB/EC/RE/Regulatory Authority approval letter(s) or CRS's memo do not contain enough information to be linked to the most current DAIDS- approved version of the protocol, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

2. Regulatory Entity (RE)/Regulatory Authority Approvals

When other approvals are required in addition to the reviewing IRB/EC at a CRS prior to implementation of a protocol at a CRS, copies of those approval letters and any other appropriate correspondence (as noted in Section 1 above) must be submitted to the DAIDS PRO with registration materials.

NOTE: *If a given RE/Regulatory Authority requires review/approval of initial versions of protocols but does not review and approve full version amendments and LOAs, the CRS Leader or IOR should provide letter/documentation from the Regulatory Authority or by submission of the applicable regulation that defines the specific requirement when submitting registration materials. The CRS Leader or IOR must document in writing to the DAIDS PRO and also provide documentation (letter from the entity or SOP/guidance/regulation/procedure document of the entity) that shows that the entity doesn't review/approve full version protocol amendments/LOAs/Site specific ICs, when submitting registration materials*

NOTE: *In addition to U.S. FDA requirements, DAIDS requires that all sites participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials list all authorities that must review/approve/acknowledge the clinical trial prior to implementation at a CRS. These regulatory entities may include any authorities that regulate, provide permits and/or provide authorization before commencing any clinical trial at a CRS. For information on completing the Form FDA 1572 and/or DAIDS IOR Form, refer to Section V, Sub Sections A and B - "Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/Regulatory Authority(ies) and Institutional Biosafety Committees (IBCs)"*

3. Clinical Trial Applications (CTA) for In-country Regulatory Entity (RE)/Regulatory Authority(ies)

DAIDS requires the submission of Clinical Trials Applications (CTAs) to DAIDS to ensure compliance with ICH E6. DAIDS requires that a copy of the CTA submitted to the competent National Regulatory Authority(ies) be submitted to the DAIDS RSC to verify the accuracy of the application/submission prior to sites being allowed to complete the initial protocol registration process for a protocol. Refer to the Clinical Trial Application Submission Guidance on how to submit CTA documents to the DAIDS RSC.

Per the DAIDS Policy for Protocol Registration (DWD-POL-RA-011), the in-country Clinical Trial Application Form/Document submitted to National Regulatory Authorities must be submitted to the DAIDS RSC prior to a CRS's being able to participate in the trial. The Clinical Trial Application Form/Document is required for National Regulatory Authorities identified on the Form FDA 1572 or DAIDS IOR Form.

Attachments included with the applications are not required unless required to identify the sponsor and applicable protocol information. See specific document requirements and follow submission instructions as stated in the Clinical Trial Application Submission Guidance.

4. Documentation of Pediatric Risk/Benefit Category

Per the DAIDS Policy for Enrolling Children (including Adolescents) in NIAID (DAIDS)-supported and/or sponsored Human Subject Clinical Research, for research studies including children or adolescents, DAIDS requires documentation of the IRB/EC designation of the pediatric risk/benefit category per the U. S. Federal regulations, 45 CFR 46, 404-407 and 21 CFR 50.51-54 and IRB /EC approval for involvement of children based on the determination specified by that category. This requirement applies to the initial and continuing/annual reviews of research protocols and to any subsequent reviews of full version protocol amendments and LOAs involving potential study risks or benefits. The documentation may be in the IRB/EC approval letter(s) or in other official correspondence from the IRB/EC to the site Investigator.

NOTE: *Failure to submit documentation of the IRB/EC designation of the pediatric risk/benefit category or documentation that the CRS will not enroll children or adolescents at the time of registration submission to the DAIDS PRO will result in delays in protocol registration.*

F. Institutional Biosafety Committee (IBC) Approval

REQUIRED FOR ALL INITIAL REGISTRATIONS FOR RESEARCH THAT INVOLVES RECOMBINANT DNA.

Research supported by NIH funding that involves recombinant DNA is subject to special regulatory oversight by an IBC. In addition, clinical trials testing products containing recombinant DNA must be submitted to the NIH Office for Biotechnology Activities (OBA) for review by the NIH Recombinant DNA Advisory Committee (RAC). Detailed information regarding the requirements for NIAID (DAIDS) -sponsored and/or -supported research involving recombinant DNA is available on the DAIDS RSC website under the “Protocol Registration” section.

Once IBC approval is received, a copy of the final approval letter and any other appropriate correspondence (as noted in Section 1 above) must be submitted to the DAIDS PRO with the initial registration submission. Failure to submit documentation of IBC approval at the time of initial registration submission to the DAIDS PRO will result in delays in protocol registration.

If an IBC must review and approve all full version protocol amendments and LOAs prior to the implementation at a CRS, documentation of the IBC approval should be submitted to the DAIDS PRO at the time of amendment or LOA registration.

All IBC approval letter(s) must be able to be linked to the current DAIDS- approved version of the protocol at the time of initial protocol registration. Since not all IBCs include the DAIDS-required identifying information in their approval letters, a CRS can submit a memo with their IBC submission which lists identifying information corresponding to the protocol, all the documents submitted for review as well as the date of submission to the IBC. The required identifying information are:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS sample informed consent forms.

- DAIDS ES and/or Network Protocol ID Number.

- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS AND/OR the final version date of the protocol document approved by DAIDS.

The CRS's memo can be used to document that the IBC received the correct version of the protocol and may be included with the IBC approval letter that is submitted to DAIDS PRO.

NOTE: *The CRS's memo to the IBC requesting review must pre-date the date on the final IRB/EC approval letter(s).*

NOTE: *If the IBC approval letter or CRS's memo does not contain enough information to be linked to the most current DAIDS-approved version of the protocol, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

G. Protocol Signature Page (PSP)

REQUIRED FOR ALL INITIAL, AMENDMENT, LOA, AND CHANGE OF IOR SUBMISSIONS

DAIDS has implemented a new regulatory requirement effective May 07, 2017 a Protocol Signature Page (PSP) to document the commitment of the IOR to conduct the trial in compliance with the protocol as agreed to by the sponsor and in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

NOTE: *DAIDS does not require submission of the PSP to an IRB/IEC or regulatory authority, unless required by the IRB/EC/RE.*

The following language must be included in all PSPs:

"I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies."

A site should not alter the above template language but may add required language (e.g., institutional requirement) for the IORs commitment to conduct the trial in accordance with all applicable regulations.

All PSPs must be able to be linked to the current DAIDS- approved version of the protocol at the time of protocol registration. The required identifying information are:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS sample.
- DAIDS ES and/or Network Protocol ID Number.
- DAIDS Protocol Version Number (including LOA version when applicable) for the version being registered.
- DAIDS Protocol Version Date for the version being registered.

All PSPs must be signed by the DAIDS approved IOR listed on the Form FDA 1572/DAIDS IOR Form. The PSP is protocol-specific and must be signed by the IOR at each participating site. This responsibility may not be delegated. If there are more than one IOR, a PSP is required for each IOR or a Single PSP can be submitted that is independently signed and dated by each IOR. If there is changes of IOR, an updated PSP is required as part of the Change of IOR submission. All original PSPs must be maintained in the regulatory binder at the site.

NOTE: *Failure to include s signed PSP at the time of submission to the DAIDS PRO will result in processing delays until the required document is received.*

NOTE: *Electronic Signature are permissible using 21 CFR 11.1compliant signatures. Security certificates associated with your digital signatures should be maintained at the site in compliance with 21 CFR 11.1(a). If utilizing electronic signatures, the date listed in the date filed should be the same date identified on the electronic signature. For additional information regarding electronic signatures, please see the Signature Requirement Guidance.*

NOTE: *If handwritten signatures are used, the date must also be handwritten.*

H. Suspension or Termination of IRB/EC Approval

Per U.S. federal regulations, 45 CFR 46.113 the IRB/EC has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's/EC's requirements or that has been associated with unexpected serious harms to participants. The regulations mandate that when the reviewing IRB/EC suspends or terminates its approval of research, this information be reported to, among others, the investigator and sponsor.

Per the DAIDS Critical Events Manual, for any studies that are protocol registered through the DAIDS PRO, the CRS must submit documentation of the suspension or termination of IRB/EC approval to DAIDS as soon as possible, but not later than 3 reporting days through the DPRS. If a study is not registered through the DAIDS PRO, the CRS must notify the appropriate DAIDS Program Officer (PO) or Contracting Officer Representative (COR) of the IRB/EC actions to suspend or terminate IRB/EC approval.

I. Site-Specific Informed Consent Forms (ICFs)

REQUIRED FOR:

- ALL INITIAL, FULL VERSION PROTOCOL AMENDMENT and LOA REGISTRATIONS
- CONTINUING /ANNUAL REVIEW SUBMISSIONS
- SITE-INITIATED REVISIONS TO SITE-SPECIFIC ICFs, and IF THERE WAS A CHANGE TO THE SITE-SPECIFIC ICFs
- SUBMISSION OF REVISED SITE ICFs IN RESPONSE TO A DISAPPROVAL NOTIFICATION.

Site-specific ICF(s) must contain all information necessary to comply with U.S. federal regulations, local laws and regulations, ICH and DAIDS policies. This includes all the basic and additional elements, as outlined in U.S. federal regulations, 45 CFR 46.116 and 21 CFR 50.25. To assist sites with developing their site-specific ICF(s), DAIDS works with the Protocol Teams to create sample ICFs that contain all the specific elements required by the U.S. federal regulations, 45 CFR 46.116 and 21 CFR 50.25.

A CRS must submit to the DAIDS PRO a copy of all site-specific ICF(s) that will be used during the informed consent process at the site after review and approval by the IRB/EC and other applicable Regulatory Entity (RE)/Regulatory Authority(ies). and retain the original(s) on file at the site.

All materials that are used in the informed consent process (e.g., ICFs, questionnaires, etc.) that are given to participants should be submitted to DAIDS for sponsor files along with any approvals (if any) IRB/EC/ RE of these documents.

If there any Sample ICFs provided with the final DAIDS approved version of the protocol that will *not* be needed at a CRS, (i.e., if a pregnancy ICF is not needed because pregnant women will not be enrolled), the CRS must document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with the registration submission.

If a Sample ICF is removed as part of an amended protocol and the site will no longer be using the consent form, a memo or note must be included with the Amendment registration submission declaring that the specific consent form will no longer be utilized at the site.

When an IRB/EC/ RE/Regulatory Authority(ies). approves a site-specific ICF and the site contact information is left blank, the CRS must include a memo with their registration submission explaining that the CRS will insert the site-specific contact information prior to consenting participants.

If an IRB/EC/RE/Regulatory Authority(ies) requires language in a site-specific ICF specific to the institution or based on local regulations/requirements, the site should include that information in the site-specific ICF and must provide documentation from IRB/EC/RE regarding the required language in the site-specific ICF. However, even though an IRB/EC/RE requires language in site-specific ICF, none of the basic and additional elements found in the DAIDS approved Sample ICF or required by DAIDS policy should be removed. Refer to the Frequently Asked Questions and the Informed Consent Process Information on the DAIDS RSC website for additional information regarding the development of site-specific ICFs.

If a CRS deletes or makes any substantive change to basic and/or additional elements as presented in the DAIDS-approved Sample ICF, the IOR or designee for the clinical trial must provide written documentation to explain the deletions/change(s) at the time of registration submission to the DAIDS PRO.

All site-specific ICF(s) must be able to be linked to the current DAIDS approved version of the protocol. The DAIDS-required identifying information are:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS-approved Sample ICF forms.

- DAIDS ES and/or Network Protocol ID Number.

- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS and/or the final version date of the protocol document approved by DAIDS.

NOTE: *For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable REs/Regulatory Authority(ies)), CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the DAIDS protocol version number and/or the final version date of the DAIDS-approved protocol must remain on all site-specific ICFs as well.*

NOTE: *If any of the site-specific ICF(s) do not contain enough information to be linked to the most current DAIDS-approved version of the protocol, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

J. Types of ICFs and Protocol Registration Requirements

Main ICF - The Main ICF issued for enrollment of participants into the protocol. The Main ICF should include all of the basic and appropriate additional elements as outlined in U.S. federal regulations, 45 CFR 46.116 and 21 CFR 50.25. The link to OHRP's guidance on informed consent form required elements can be found here.

Screening and Stored Specimen ICFs - The following are DAIDS requirements regarding generic screening and stored specimen consent forms and protocol- specific screening consent forms.

Generic screening and stored specimen ICF - A generic screening and/or stored specimen ICF is an ICF that is developed by a CRS for its own purposes and not related to any DAIDS requirement and should NOT be submitted to the DAIDS PRO. The DAIDS PRO will NOT review or approve any such generic screening and/or stored specimen ICFs if they are submitted with registration materials.

Protocol-specific screening and stored specimen ICF - A protocol-specific screening and/or stored specimen ICF is an ICF developed for a specific protocol that is approved by DAIDS and is included as part of the final protocol and DAIDS-approved Sample ICFs. If the DAIDS-approved Main ICF includes screening procedures and stored specimen information and a CRS chooses to develop a separate protocol-specific screening and/or stored specimen ICF to be used at the site, then the screening and eligibility and/or stored specimen information can be removed from the site-specific main ICF. In this instance, the CRS must submit BOTH the protocol-specific screening and/or stored specimen ICF and the site-specific main ICF to the DAIDS PRO for review and approval.

Short ICFs - If a CRS elects to use a short ICF in addition to the main ICF, the CRS must have a main ICF OR written summary that includes all the required basic and appropriate additional elements which have been approved by the IRB/EC and has been submitted to the DAIDS PRO for registration. A CRS must receive a Registration Notification from the DAIDS PRO for all short form ICFs prior to implementation.

Sub-study ICFs - If a NIAID (DAIDS)-supported and/or-sponsored protocol includes a separate DAIDS-approved Sample ICF for a sub-study that is part of the main protocol and the CRS anticipates participating in the sub-study, the CRS must include the sub-study site-specific ICF in their protocol registration submission. A CRS must receive a Registration Notification from the DAIDS PRO for all sub- study ICFs prior to implementation.

Pregnancy ICF - If a DAIDS-supported and/or sponsored protocol includes a DAIDS-approved Sample ICF for women who become pregnant while on study and the CRS anticipates that some pregnant women may be included or followed on the study, the CRS must submit the site-specific pregnancy ICF to the DAIDS PRO.

Sites have the flexibility to combine the pregnancy ICF and the main ICF into one ICF, as long as the required information is still present, and this approach is approved by the IRB/EC. If one or more ICFs are combined, there should be a note to the DAIDS PRO documenting why one of the original consents is not included in the registration submission.

If the site will not follow or enroll pregnant women, the pregnancy ICF does not need to be submitted, and the site should document the plan not to include pregnant women with a note to the DAIDS PRO. A CRS must receive a Registration Notification from the DAIDS PRO for any pregnancy ICF prior to implementation.

Assents - The IRB/EC must determine that adequate provisions are made for soliciting the assent of children and/or adolescents when in the judgment of the IRB/EC the children and/or adolescents are capable of providing it, 45 CFR 46.408. The IRB/EC is responsible for determining the age of assent and for determining whether the use of an assent form is appropriate. A CRS must receive a Registration Notification from the DAIDS PRO for all assents prior to implementation.

1. Health Insurance Portability and Accountability Act (HIPAA) - Privacy Rule

The Privacy Rule is a U.S. federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information.

The DAIDS PRO does not review site-specific ICFs for information related to HIPAA. If the site-specific ICF(s) contains language pertaining to HIPAA authorization, the DAIDS PRO will NOT assess this language for Privacy Rule compliance.

In addition, it is very important that confidentiality language included in the DAIDS-approved sample informed consent remain in the site-specific ICF even if this information is included in a separate HIPAA authorization form.

NOTE: *The HIPAA regulations do not apply to non-U.S. CRSs.*

Information related to the Privacy Rule can be found at the following HHS website.

2. ClinicalTrials.gov Informed Consent Requirements

ClinicalTrials.gov is the clinical trial registry databank maintained by the NIH National Library of Medicine (NLM) which was created by statute outlined in the Food and Drug Administration Amendments Act of 2007 (FDAAA). Through FDAAA, the U.S. Food and Drug Administration (FDA) amended current informed consent regulations (21 CFR 50.25) to now require that all informed consent documents for applicable drug (including biological products) and device clinical trials include a specific statement that clinical trial information will be entered into ClinicalTrials.gov. As of December 1, 2011, for new protocols, the following language **MUST** be included in the DAIDS-approved sample ICF for applicable trials:

"A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time."

The DAIDS PRO will review site-specific ICFs for information related to clinicaltrials.gov. If the DAIDS-approved Sample ICF contains the clinicaltrials.gov language, then the language MUST be in all site-specific informed consents for that study. Failure to include this language exactly as stated above in all applicable Site ICFs will result in an Approval with Required Corrections notification.

NOTE: *Per U.S. federal regulations, this language cannot be modified.*

NOTE: *Participants do not need to be re-consented for existing or ongoing studies unless the IRB/EC determines otherwise.*

NOTE: *The required language can be translated into local language.*

NOTE: *If the inclusion of the ClinicalTrials.gov language is mandated by the IRB/EC/RE (for non-applicable trial), documentation from the IRB/EC/Regulatory Authority mandating the statement inclusion must be provided to the DAIDS PRO.*

Information related to the informed consent requirement for clinicaltrials.gov can be found on the following HHS website.

K. Translation requirements

For all documents that require translation to a language other than Spanish, a CRS must submit to the DAIDS PRO a copy of the DAIDS Protocol Registration Translation Confirmation Document, attesting that the translation is a true and accurate reflection of the local language documents that have been reviewed and approved by the IRB/EC and other REs/Regulatory Authority.

In addition, sites must submit a translation certificate or its equivalent (i.e., a signed and dated documentation by the translator/translators attesting that the translation is a true and accurate interpretation of the local language document).

NOTE: CRSs are not required to complete the DAIDS Protocol Registration Translation Confirmation Document for any protocol registration documents in Spanish.

An electronic copy of the DAIDS Translation Confirmation Document can be found on the DAIDS RSC Website under the "Protocol Registration" section.

1. Form FDA 1572, IOR Form, CVs, and Medical Licenses

All Form FDA 1572s, DAIDS IOR Forms, CVs and Medical Licenses must be prepared in English. Non-English versions of these documents will not be accepted by the DAIDS PRO.

2. IRB/EC, other RE/Regulatory Authority, and IBC approval letters

All non-English IRB/EC, other applicable RE/Regulatory Authority, and IBC approval letter(s) must be translated into English, except for Spanish. CRSs must submit copies of both the local language and translated English approval letter(s) to the DAIDS PRO.

NOTE: *CRSs should provide an English translation of any other appropriate IRB/EC/RE/IBC documentation that explains changes/deletions in the site specific ICFs or that could assist the DAIDS PRO when reviewing registration materials.*

3. Site-specific ICFs

CRSs must prepare site-specific ICFs in all languages in which they will conduct informed consent discussions for each study. If CRSs elect to use short ICFs in addition to the Main ICF, the short ICF must also be prepared in all languages in which the informed consent discussions will be conducted. After approval by all applicable IRBs/ECs and REs, copies of the approved site-specific ICFs must be submitted to the DAIDS PRO.

If informed consent discussions will be conducted in English and another local language, including Spanish, the site-specific English and local language ICFs must be submitted to the DAIDS PRO. No back-translations are required by DAIDS.

If informed consent discussions will be conducted in a local language other than English or Spanish, site-specific local language ICFs must be submitted to the DAIDS PRO. Back-translations (into English) of the site-specific local language ICFs for which discussion will be conducted also must be submitted to the DAIDS PRO.

NOTE: *If a DAIDS Clinical Trials Network has specific requirements regarding translation of site-specific ICFs, the CRS should follow those requirements as well as any applicable translation and back-translation requirements specified in institutional policies, the study protocol, and/or the network Manual of Operations.*

NOTE: *Site specific ICFs in languages that were not submitted with the original initial registration should be submitted as additional ICF language type within DPRS and will be considered initial registration in the newly submitted language type.*

4. Clinical Trial Application (CTA) Form/Document

All non-English Clinical Trial Application Form/Documentation must be translated into English, except for Spanish. Copies of both the local language and translated English applications must be submitted to the DAIDS RSC along with the translation certificate and the Translation Confirmation Document (TCD).

VI. Protocol Registration Submissions

Prior to implementing a protocol and enrolling participants, a CRS must receive final approval for the site-specific ICFs from the IRB/EC and other applicable REs/Regulatory Authority(ies). In addition, the CRS must successfully complete the DAIDS initial protocol registration process. However, successfully completing the DAIDS initial protocol registration process does not authorize a CRS to begin enrollment of participants. CRSs will be notified by the appropriate DAIDS scientific program (i.e., Program Officer), Operations Center or Data Management Center when enrollment may begin for a protocol.

Each CRS will complete the protocol registration process for all clinical research supported and/or sponsored by DAIDS that is reviewed by DAIDS Scientific Review Committees, namely the Prevention Sciences Review Committee (PSRC) and the Clinical Sciences Review Committee (CSRC) and if it is determined protocol Registration is required. Upon receiving final IRB/EC and other applicable RE/Regulatory Authority approval(s), the CRS will submit all required registration documents to the DAIDS PRO via the DAIDS DPRS.

Upon making ANY submission to the DAIDS PRO, a CRS will receive a Confirmation of Submission notice that indicates successful submission of materials to the DAIDS PRO. If a CRS does not receive a Confirmation of Submission notice within 24 - 48 hours of submitting materials, the CRS should contact the DAIDS PRO.

The CRS must place a copy of all final Protocol Registration notifications from the DAIDS PRO in the site's regulatory files. Refer to Definitions of this manual for a list of final registration notifications.

A. Initial Registration

A CRS that has **not previously** received a Registration Notification from the DAIDS PRO for any version of the protocol must complete the initial protocol registration process.

If a CRS has previously received a DAIDS PRO Registration Notification for one language (i.e., English) and later submits registration documents for a new language (i.e., Spanish), the new language should be submitted as an Additional ICF Language submission type but will be considered an initial registration as this is the first time the specific language has been submitted to the DAIDS PRO for review.

If a CRS has previously received a Registration Notification from the DAIDS PRO for one informed consent type (e.g., main, pregnancy) and later submits registration documents for a new informed consent type (e.g., stored specimen, short form), the new informed consent type should be submitted as an Additional ICF Type but is considered an initial registration as this is the first time the informed consent form has been submitted to the DAIDS PRO for review.

NOTE: *If a CRS has previously received a Registration Notification from the DAIDS PRO and is only submitting an additional language or informed consent type, the site is NOT required to resubmit the Form FDA 1572/DAIDS IOR Form and the IOR CV with the protocol registration submission.*

The following documents **must** be submitted to the DAIDS PRO for all initial registration submissions:

- A copy of the Form FDA 1572 signed and dated by the IOR (for studies conducted under an IND) OR a copy of the DAIDS IOR Form signed and dated by the IOR (for non-IND studies).
- Investigator of Record CV and other required documentation (current medical license or equivalent).
- Protocol Signature Page (PSP).
- A copy of the CRS's IRB/EC and other applicable RE/Regulatory Authority approval letter(s) (see IRB/EC Approvals" of this manual)
- A copy of the IRB/EC and other applicable RE/Regulatory Authority approved site-specific ICFs (all languages including English translations, if applicable). Refer to Translation requirements" of this manual.
- A copy of the CRS's IBC approval letter, if applicable.
- Clinical Trial Application Form/Document for the site and study
- A copy of the CRS's IRB/EC/Regulatory Authority submission letter(s).
- A copy of all correspondence between the CRS and IRB/EC/Regulatory Authority
- Translation Certificate (if applicable).
- Translation Confirmation Document (if applicable).

NOTE: *If an initial registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual. Not submitting all documentation may delay registration.*

When all required documents have been received and reviewed, a CRS will receive a Registration Notification from the DAIDS PRO that will include all languages and informed consent types that have been submitted. The Registration Notification from the DAIDS PRO indicates successful completion of the initial protocol registration process.

If a CRS receives a Registration with Required Corrections Notification, a CRS must make the required corrections and submit them to their IRB/EC for review and approval OR must submit justification for why the required correction(s) will not be made to the DAIDS PRO within 120 calendar days of the date the Required Corrections Notification was issued. For information on how to submit required corrections refer to Registrations with Required Corrections" of this manual.

NOTE: *The 120 calendar days is for submission of IRB/EC approved corrections OR justifications for why the corrections will not be made to the DAIDS PRO.*

Upon successful completion of the DAIDS PRO initial registration process, indicated when a CRS receives a Registration Notification or a Registration with Required Corrections Notification, a CRS will begin receiving safety information for the protocol (i.e., safety reports, safety memos, investigator's brochures, etc.) from the DAIDS RSC Safety Information Center.

If a site-specific ICF(s) does not include all the required basic and appropriate additional elements to comply with U.S. Federal Regulations and DAIDS policies, designated CRS personnel (i.e., CRS Coordinator, IOR) will be notified via a Disapproval Notification from the DAIDS PRO regarding the deficiencies. The Disapproval Notification will outline the deficiencies in the site-specific ICF(s) that must be revised/corrected before a final Registration Notification can be issued.

NOTE: *A Disapproval Notification is not a final notification and DOES NOT indicate successful completion of the protocol registration process.*

For information on the options a CRS has upon receipt of a Disapproval Notification from the DAIDS PRO, refer to VI of this manual.

B. Amendment Registrations

1. Full Version Protocol Amendment Registration

A full version "Protocol Amendment" is a revision to a protocol made by the Protocol Team/Chair/Awardee that requires DAIDS review and final approval/sign-off before implementation. The changes to the protocol are incorporated into the protocol document and will result in a change to the DAIDS protocol version number (e.g., 2.0, 3.0). Sites should refer to the protocol document for information on the protocol registration process for full version protocol amendments.

CRSs should submit the amended protocol, DAIDS-approved Sample ICF(s), and the amended site-specific ICF(s) to their IRBs/ECs/REs and other applicable Regulatory Authority(ies) for review and approval as soon as possible. Per the DAIDS Protocol Registration policy, submission to the reviewing IRB/EC must take place within 45 calendar days for U.S. sites and 75 calendar days for non-U.S. sites of the date the amendment was approved by DAIDS and distributed to the sites.

NOTE: *The 45 or 75 calendar day requirement for submission of full version protocol amendment registration materials is for reviewing IRB/EC only.*

Amendments including any revised site-specific ICF(s) must be implemented immediately (i.e., without delay no later than 5 business days, usually at the participant's next scheduled study visit) upon CRS receipt of all required IRB/EC/ RE/Regulatory Authority(ies)approvals unless the amendment specifies otherwise. DAIDS PRO approval notification is not required for amendments unless specified in the protocol.

The CRS may delay implementing an amendment when the IRB/EC/ RE/Regulatory Authority(ies) approved amendment states the protocol changes will be implemented once specific operational issues (i.e., training on new procedures added in the amendment) are addressed. The IRB/EC/ RE/Regulatory Authority(ies) documentation must be kept in the site's regulatory files for verification by monitors.

When the IRB/EC/ RE/Regulatory Authority(ies) approved amendment and revised site-specific ICFs are not implemented immediately after final IRB/EC/ RE/Regulatory Authority(ies) approval, sites may continue conducting protocol related interactions and interventions with already enrolled study participants under the previously approved version as long as the IOR has determined that this is in the participant's best interest. After receiving final IRB/EC/ RE/Regulatory Authority(ies) approval and while operational issues are being addressed, new participants may only be enrolled under the previously approved version of the site-specific ICFs when the IRB/EC/RE/Regulatory Authority(ies). has determined this is acceptable. The IRB/EC/ RE/Regulatory Authority(ies) determination should be documented in writing and filed in the site's regulatory files.

A CRS must submit full version protocol amendment registration documents to the DAIDS PRO within 14 calendar days of the CRS's receipt of all the required final written IRB/EC approval documentation for the amendment. The submitted documents must include documentation of the date the amended protocol and any revised site-specific.

NOTE: *Sites are strongly advised to document the date the CRS receives each final* IRB/EC/ RE/Regulatory Authority(ies) *approval letter. Documenting this information supports the CRS's action to comply with the DAIDS protocol registration policy regarding submission of amendment and LOA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final* the IRB/EC/RE/Regulatory Authority(ies) *approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.*

If a CRS has received a Registration Notification from the DAIDS PRO for an earlier version of the protocol including all informed consent types and specific language(s), then the registration to a new version of the protocol would be a full version protocol amendment. A CRS that has never received a Registration Notification from the DAIDS PRO for any version of the protocol, language or informed consent type must follow the instructions for Initial Registration of this manual.

NOTE: *If a CRS has submitted a registration packet for a previous version of a protocol prior to a new version being approved by DAIDS and distribution to the sites, the DAIDS PRO will continue to process the registration for the earlier version.*

The following documentation must be submitted to the DAIDS PRO for all full version protocol amendment registration submissions:

- A copy of the site's IRB/EC and other applicable RE/Regulatory Authority approval letter(s)

Refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual for detailed information.

- Documentation of the date the amended protocol and any revised site- specific ICF(s) were submitted to the reviewing IRB/EC.

- Protocol Signature Page (PSP) to document the commitment of the IOR(s) to conduct the trial in compliance with regulations/laws.

- A copy of the IRB/EC/RE and other applicable Regulatory Authority (ies) approved site ICF(s) (all languages including English translations, if applicable). Refer to section V, "Translation Requirements" of this manual.

- A copy of the CRS's IBC approval letter, if applicable

- Any amended (if applicable) in-country Clinical Trial Application Form/Document for all applicable entities. See the Clinical Trial Application Submission Guidance on DAIDS RSC website for additional information.

- A copy of the CRS's IRB/EC and other applicable /Regulatory Authority(ies) submission letter(s).

- A copy of all correspondence between the CRS and IRB/EC and other applicable RE/Regulatory Authority(ies).

- Translation Certificate (if applicable).

- Translation Confirmation Document (if applicable).

NOTE: *If any Site Specific ICFs registered in the previous version will no longer be utilized at the site, documentation must be submitted that states that the Site Specific ICFs will no longer be utilized at the site.*

NOTE: *Examples of appropriate documentation of the date the amended protocol and any revised site-specific ICF(s) were submitted to the reviewing IRB/EC includes but is not limited to the submission letter from the site to the IRB/EC, a memo from the IOR or designee specifying the date of submission to the IRB/EC.*

NOTE: *If the IRB/EC determines that a full version protocol amendment does not require changes to the site-specific ICF(s), the CRS should document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with the full version protocol amendment registration submission. Otherwise, all previously registered Site Specific ICF types must be submitted with the amended version or Justification for the omission of Site Specific ICF type must be provided. Documentation of approval of the amended protocol is still required from of the site's IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s) and any other appropriate documentation from the IRB/EC and other applicable RE/Regulatory Authority(ies) regardless of whether the site specific ICFs were revised.*

NOTE: *Re-consenting participants as a result of amendment (Change or new information that may affect subject participation) is the decision of the CRS's IRB/EC. CRSs should follow their IRB/EC/RE/ Regulatory Authority instructions for re- consenting participants as a result of a full version protocol amendment. For additional information regarding re-consenting see the DAIDS Memo Regarding Timing of Consent and Re-Consent with Updated IRB/EC/RE-Approved Consent Forms on the DAIDS RSC website Site Informed Consent Process Information.*

NOTE: *If a full version protocol amendment registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to "Requested Materials" of this manual.*

When all required documents have been received and approved, a CRS will receive a Registration Notification from the DAIDS PRO that will include all languages and informed consent types that have been submitted. The Registration Notification from the DAIDS PRO indicates successful completion of the full version protocol amendment registration process.

NOTE: *A Registration Notification from the DAIDS PRO is NOT required prior to implementing a full version protocol amendment at a CRS.*

NOTE: *Once a new version of a protocol is approved by DAIDS and has been distributed to the sites, a CRS will no longer be able to register for a previous version.*

2. Letter of Amendment (LOA) Registration

CRSs should submit the LOA and any amended site-specific ICF(s) to their IRBs/ECs and other applicable REs/ Regulatory Authority (ies) for review and approval as soon as possible. Per the DAIDS Protocol Registration policy, submission to the reviewing IRB/EC must take place within 45 calendar days for U.S. sites and 75 calendar days for non-U.S. sites of the date the LOA was approved by DAIDS and distributed to the sites.

NOTE: *The 45 or 75 calendar day requirement for submission of LOA materials is for reviewing*
IRB/EC only.

NOTE: *Protocol revisions resulting from LOAs DO NOT affect the DAIDS protocol version. For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable Regulatory Authority(ies)/Regulatory Authority(ies), CRSs can specify the site (local version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the DAIDS protocol version number and/or the final version date of the DAIDS-approved protocol should remain on all site-specific ICFs.*

LOAs including any revised site-specific ICF(s) must be implemented immediately (i.e. without delay no later than 5 business days, usually at the participant's next scheduled study visit) upon a CRS' receipt of all required IRB/EC and RE/ Regulatory Authority approvals DAIDS PRO approval notification is not required for LOA unless specified in the LOA.

The CRS may delay implementing a LOA when the IRB/EC/ Regulatory Authority (ies)/Regulatory Authority(ies) approved LOA states the protocol changes will be implemented once specific operational issues (i.e., training on new procedures added in the LOA) are addressed. The IRB/EC/RE/Regulatory Authority(ies) documentation must be kept in the site's regulatory files for verification by monitors.

When the IRB/EC/ RE/Regulatory Authority(ies) approved LOA and revised site-specific ICFs are not implemented immediately after final IRB/EC/RE approval, sites may continue conducting protocol related interactions and interventions with already enrolled study participants under the previously approved version as long as the IOR has determined that this is in the participant's best interest. After receiving final IRB/EC/ RE/Regulatory Authority(ies) approval and while operational issues are being addressed, new participants may only be enrolled under the previously approved version of the site-specific ICFs when the

IRB/EC/RE has determined this is acceptable. The IRB/EC/ RE/Regulatory Authority(ies) determination should be documented in writing and filed in the site's regulatory files.

A CRS must submit LOA registration documents to the DAIDS PRO within 14 calendar days of the CRS's receipt of all the required final written IRB/EC approval documentation for the LOA. The submitted documents must include documentation of the date the LOA and any revised site-specific ICF(s) were submitted to the reviewing IRB/EC. The DAIDS PRO will not review any revised site-specific ICF(s) unless otherwise noted in the LOA.

NOTE: *Sites are strongly advised to document the date the CRS receives each final IRB/EC/ RE/Regulatory Authority(ies) approval letter. Documenting this information supports the CRS's action to comply with the DAIDS protocol registration policy regarding submission of amendment and LOA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final IRB/EC/ RE/Regulatory Authority(ies) approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.*

The following documentation must be submitted to the DAIDS PRO for all LOA registration submissions:

- A copy of the site's IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s)for all Entity(ies) listed on the FDA Form 1572/DAIDs IOR Form (refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual for detailed information on IRB/ RE/Regulatory Authority(ies))

- Documentation of the date the LOA and any revised site-specific ICF(s) were submitted to the reviewing IRB/EC.

- Protocol Signature Page (PSP) to document the commitment of the IOR(s) to conduct the trial in compliance with regulations/Laws

- A copy of the IRB/EC and other applicable RE/Regulatory Authority(ies) approved site ICF(s) (all languages including English translations, if applicable). Refer to Translation requirements" of this manual.

- A copy of the CRS's IBC approval letter, if applicable.

- A copy of the CRS's IRB/EC and other applicable RE/ Regulatory Authority submission letter(s).

- A copy of all correspondence between the CRS and IRB/EC and other applicable RE/Regulatory authorities.

- Translation Certificate (if applicable).

- Translation Confirmation Document (if applicable).

NOTE: *Examples of appropriate documentation of the date the LOA and any revised site-specific ICF(s) were submitted to the reviewing IRB/EC includes but is not limited to -*

- *the submission letter from the site to the IRB/EC.*
- *a memo from the IOR or designee specifying the date of submission to the IRB/EC.*

NOTE: *Re-consenting participants as a result of LOA (Change or new information that may affect subject participation) is the decision of the CRS's IRB/EC. CRSs should follow their IRB/EC/ RE/Regulatory Authority(ies)instructions for re- consenting participants as a result of the LOA.*

NOTE: *If a LOA registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

When all required documents have been received, a CRS will receive a Registration Notification from the DAIDS PRO for each LOA registration submission. The Registration Notification from the DAIDS PRO indicates successful completion of the LOA registration process.

NOTE: *LOAs are considered individual amendments to a protocol. Thus, sites must protocol register to all LOAs independent of initial and full version amendment registrations. If a site elects to include a LOA as part of another submission to the IRB/EC/ RE/ Regulatory Authority(ies) (i.e., continuing review, amendment review, and initial review) the site must clearly document all the materials that are being submitted to the IRB/EC/ RE/Regulatory Authority(ies) for review and approval. It is a CRS's responsibility to inform the DAIDS PRO regarding all registrations (i.e., LOA, full version amendment, initial, continuing review) the site is requesting at the time of submission. Failure to register to a LOA may result in a CRS being out of compliance with DAIDS policies and may result in delays in implementing operational changes triggered by LOA registrations.*

NOTE: *All submission types (Initial, Full Version Amendment, LOA) must be submitted independently.*

NOTE: *A Registration Notification from the DAIDS PRO is NOT required prior to implementing a LOA at a CRS.*

C. Sub-Study Registration

A CRS must protocol register to all sub-studies that have a protocol number and/or DAIDS protocol identification number if a site anticipates enrolling participants. A CRS will receive a registration notification for each sub-study that is submitted for protocol registration. CRSs must register to embedded sub-studies as part of the main study registrations. Registration for embedded sub-studies is required for all versions of the main study unless the site informs the DAIDS PRO that they are no longer participating in the embedded sub-study and request deregistration. CRSs should register to stand alone sub-studies as separate registrations and can be done independently from the main study registration. A CRS registering to a stand-alone sub-study is required to submit all required documents (i.e., IRB/EC approval letter(s), site-specific consent(s), Form FDA 1572 and/or DAIDS IOR Form, and IOR CV) when registering to a stand- alone sub-study.

NOTE: *For an explanation of embedded and stand-alone sub-studies refer Definitions of this manual.*

D. Other Submissions

Other submissions are ANY submissions made to the DAIDS PRO that are not Initial, Full Version Amendment or LOA registrations. Below is detailed information on requirements related to “other submissions” a CRS may submit to the DAIDS PRO.

1. Requested Materials

Requested materials are additional and/or corrected materials requested by the DAIDS PRO as a result of an incomplete submission to the DAIDS PRO. If any required documents are missing, incomplete, or are inaccurate, the DAIDS PRO will issue a Requested Materials notice to designated CRS personnel (i.e. CRS Coordinator, IOR). ***This request will stop the registration review process.***

NOTE: *The Protocol Registration review process will not continue until all Requested Materials have been received by the DAIDS PRO.*

A copy of the requested materials must be submitted to the DAIDS PRO in response to a Materials Request Notification as a “materials Request” type submission.

A CRS will receive a Confirmation of Submission notice once the requested materials have been received by the DAIDS PRO.

2. Disapprovals

If it is determined during the DAIDS PRO review process that a site-specific ICF(s) does not include all the required basic and appropriate additional elements to comply with Federal Regulations and DAIDS policies, designated CRS personnel (e.g., CRS Coordinator, IOR)

will be notified via a Disapproval Notification from the DAIDS PRO regarding the deficiencies. The disapproval notification will outline the deficiencies in the site-specific ICF(s) that must be revised or corrected before a final Registration Notification can be issued.

Upon receipt of a Disapproval Notification from the DAIDS PRO a CRS has two options:

1. Make the necessary revisions/corrections and submit the revised document(s) to their IRB/EC and other applicable RE/Regulatory Authority(ies) approval(s) for review and approval. Upon receiving final IRB/EC/ RE/Regulatory Authority(ies) approval for the revised document(s) the CRS must make a "Corrected Materials" submission to the DAIDS PRO, or

2. Submit justification for the omission/changes to the DAIDS PRO via a request for Disapproval Reversal.

Under Option 1 - The following documentation must be submitted to the DAIDS PRO as “Corrected Materials” once a CRS receives final IRB/EC and other applicable RE/ Regulatory Authority approval for the revised document(s) -

- A copy of the site’s IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s) and any other appropriate documentation from the IRB/EC other applicable REs/ Regulatory Authority (ies).

  NOTE: *For examples of other appropriate IRB/EC/RE/Regulatory Authority(ies) documentation refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals” of this manual.*

- A copy of the IRB/EC and other applicable RE/Regulatory Authority(ies) approved revised site-specific ICF(s).

When ALL required documents have been received and it is confirmed that the required corrections have been made, the DAIDS PRO will issue a Registration Notification.

Under Option 2 - If a CRS believes that a Disapproval Notification has been issued in error, the CRS can submit a request for Disapproval Reversal. A CRS must provide justification and/or documentation explaining why the disapproval should be reversed.

The following documentation must be submitted to the DAIDS PRO to request a disapproval reversal:

- Written justification and/or a copy of any documentation supporting the CRS’s request for the disapproval reversal

A CRS will be notified within 4 business working days as to whether or not the disapproval will be reversed via e-mail from the DAIDS PRO.

3. Registrations with Required Corrections

If a CRS receives a Registration with Required Corrections Notification, a CRS must make the required corrections and submit them to their IRB/EC/ RE/Regulatory Authority(ies) for review and approval OR must submit justification for why the required corrections will not be made within 120 calendar days of the date the Registration with Required Corrections Notification was issued.

A Registration with Required Corrections Notification indicates that a CRS may begin using the site-specific ICFs after protocol activation by the appropriate Operations Center, Data Management/Statistical Center or DAIDS Program.

Upon receipt of a Registration with Required Correction Notification from the DAIDS PRO a CRS has two options:

1. Make the necessary required corrections and submit them to their IRB/EC for review and approval. Upon receiving final IRB/EC and other applicable RE/Regulatory Authority(ies) approval for the corrected document(s) the CRS must make a "Corrected Materials" submission to the DAIDS PRO, or

2. Submit justification for the omission/changes via a "Corrected Materials" submission to the DAIDS PRO.

Under Option 1 - The following documentation must be submitted to the DAIDS PRO as “Corrected Materials”, once a CRS receives final IRB/EC and other applicable RE/Regulatory Authority(ies) approval for the corrected document(s):

- A copy of the site’s IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s) and any other appropriate documentation from the IRB/EC other applicable RE/Regulatory Authority(ies).

- A copy of the IRB/EC and other applicable RE/Regulatory Authority(ies) approved revised/corrected site-specific ICF(s).

NOTE: *For examples of other appropriate IRB/EC/ RE/Regulatory Authority(ies) documentation refer to IRB/EC Approvals” of this manual.*

Under Option 2 - If a CRS has believed that a Registration with Required Corrections Notification has been issued in error, the CRS can submit justification and /or documentation explaining why the Registration with Required Corrections Notification should be reversed.

The following documentation must be submitted to the DAIDS PRO as “Corrected Materials”:

- Written justification and/or a copy of any documentation supporting the CRS’s request for the Registration with Required Corrections reversal.

For Option 1 and 2, a CRS will receive an Approval of Required Corrections Notification from the DAIDS PRO when all the required corrections have been reviewed and approved. The official registration date will remain the date the Registration with Required Correction Notification was issued.

4. Administrative Registration

Administrative registrations should occur when a site is not recruiting participants in a NIAID (DAIDS)-supported and/or -sponsored clinical trial but has administrative functions only. Protocol/Grant PI/Protocol Chair/Co-Chair’s routinely make substantial study interventions (decisions and interpretations) that affect study participants even though participants may not be enrolled or seen at the Protocol/Grant PI/Protocol Chair/Co-Chair’s CRS. As a result, the Protocol/Grant PI/ Protocol Chair/Co-Chair’s institutions are considered engaged with the research and must assure compliance with applicable Department of Health and Human Services (DHHS) regulations. For more information on engagement refer to the OHRP guidance document.

Based on U.S. federal regulation 45 CFR 46.103(a), “each institution engaged" in human subject research that is supported and/or sponsored by the DHHS must provide the OHRP with a satisfactory Assurance of Compliance with the regulations, unless the research is exempt under U.S. federal regulation 45 CFR 46.101(b).

For all administrative registrations, DAIDS requires that that the Protocol/Grant PI/Protocol Chair/Co-Chair consults with their IRB/EC and receive documentation in writing of the IRB/EC's decision concerning their protocol review and approval. At least two different kinds of decisions can be made:

1. IRB/EC wants to be involved in reviewing and approving the protocol.

2. IRB/EC does not want to be involved in reviewing and approving the protocol and will rely on another IRB/EC, designated on the Federal Wide Assurance (FWA), for review and approval.

DAIDS will honor the decision of the IRB/EC. The Protocol/Grant PI/ Protocol Chair/Co-Chair (s) need to consult with their IRB/EC and obtain written documentation of the IRB/EC's decision regarding their review and approval of the protocol in order to comply with U.S. federal regulations.

Upon receipt of final approval and/or documentation from the IRB/EC, an administrative registration submission should be made to the DAIDS PRO.

The following documentation must be submitted to the DAIDS PRO for all Administrative Registrations:

- A copy of the IRB/EC approval letter *AND* any other appropriate documentation from the IRB/EC including the IRB/EC decision regarding protocol review and approval.

  NOTE: *For examples of other appropriate IRB/EC/ RE/Regulatory Authority(ies) documentation refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual.*

- A copy of the Form FDA 1572 signed and dated by the Protocol/Grant PI/Protocol Chair/Co-Chair (for studies conducted under an IND) OR a copy of the DAIDS IOR Form signed and dated by the Protocol Protocol/Grant PI/ Protocol Chair/Co-Chair (for non-IND studies)

- A copy of the Protocol/Grant PI/Protocol Chair/Co-Chair CV and corresponding Medical license/equivalent

A CRS will receive a Registration Notification from the DAIDS PRO for each administrative registration submission when all required documents have been received. The Registration Notification from the DAIDS PRO indicates successful completion of the administrative registration process.

5. Change of Investigator of Record (IOR)

When there is a change in the IOR listed in Section 1 on the Form FDA 1572 or DAIDS IOR Form, a CRS should submit a copy of the revised Form FDA 1572 or the revised DAIDS IOR Form to the DAIDS PRO. To officially change the IOR for a protocol(s), the CRS must submit the documentation within 15 calendar days of the CRS's notification that the current IOR will no longer serve as the IOR for the study. CRS must notify DAIDS when there is a change of IOR in a timely manner.

The following documentation should be submitted to the DAIDS PRO for all Change of IOR requests:

- Memo requesting a change of IOR.
- A copy of the new Form FDA 1572 signed and dated by the new IOR (for studies conducted under an IND) OR a copy of the new DAIDS IOR Form signed and dated by the new IOR (for non-IND studies).
- CV for the new IOR and other required documentation (current medical license or equivalent).
- A Protocol Signature Page for the new Investigator of Record.
- If IRB/EC or RE/Regulatory Authority(ies) approval is required to change the investigator at the CRS, the submission and approval letters from the entity(ies) is required.

A CRS will receive a Change of IOR Approval Notification from the DAIDS PRO when the change of IOR has been reviewed and approved by the DAIDS PRT.

NOTE: *The Change of IOR is NOT official until the CRS receives a Change of IOR Approval Notification from the DAIDS PRO.*

NOTE: *A CRS must notify their DAIDS Office for Clinical Site Oversight (OCSO) representative and/or DAIDS Program Officer when there is a change in CRS Leader or other key CRS site personnel and/or contact information.*

6. Continuing/Annual Review

Per the October 2018 FDA Guidance on FDA-Regulated Clinical Investigations (studies under an IND), IRB/ECs must continue to comply with current FDA requirements for IRB/ECs continuing review at 21 CFR 56.109(f), including for clinical investigations that are subject to both HHS and FDA jurisdiction. IRB/ECs are required to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (21 CFR 56.109(f)).

For studies that are NOT conducted under an IND, DHHS regulations, 45 CFR 46.109(e) require that all DHHS supported research undergo continuing IRB/EC review at intervals appropriate to the degree of risk, but NOT LESS than once per year.

As described in §46.109(f)(1)

Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research eligible for expedited review in accordance with §46.110;

(ii) Research reviewed by the IRB in accordance with the limited IRB review described in §46.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);

(iii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

(A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

(B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

NOTE: *For the continuing review implementation delay period from July 19,2018 through January 20, 2019, institutions may elect to implement certain "burden-reducing" provisions if they plan to transition their research to comply with the 2018 HHS requirements ("Revised Common Rule"). One of these provisions is the allowance for no annual continuing review of certain categories of research.*

NOTE: *Per §46.115, the IRB/EC or CRS must document the IRB/EC's transition decision (including the date of the decision). CRSs must keep this documentation in their regulatory binder at the site.*

In the above instance, if the site's reviewing IRB/EC elects to implement the burden-reducing provision and determines that a study does not require continuing review under the 2018 HHS continuing review requirements at §46.109(f))(1) and will not conduct continuing reviews annually during the delay period, sites must submit to the DAIDS PRO documentation from the IRB/EC that documents this IRB/EC determination, including reference to the applicable CFR that states the reason an annual continuing review is not required.

If an individual IRB/EC determines that a protocol meets the requirements within §46.109(f) and will not conduct continuing reviews annually, sites must submit documentation from the IRB/EC that documents the determination including reference to the applicable CFR that states the reason an annual review is not required.

For protocols that must undergo continuing review on an annual or more frequent basis, continuing review must be performed prior to the expiration date specified on the IRB/EC approval letter(s) and/or site-specific ICFs. The frequency of ongoing reviews should be documented in IRB/EC policies and procedures and may be protocol/study specific. CRSs can visit the OHRP website for additional guidance related to continuing review.

CRSs participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials, reviewed by the DAIDS Scientific Review Committees and are protocol registered are required to submit documentation of IRB/EC Continuing/Annual review approval to the DAIDS PRO. Continuing/Annual review documentation must be submitted to the DAIDS PRO within 14 days of the CRS receiving final written documentation of IRB/EC Continuing/Annual review approval. The IRB/EC approval of continuing review must be a final approval and not require any modifications or further input by the CRS.

The following documents must be submitted to the DAIDS PRO for all continuing/annual review submissions:

- A copy of the IRB/EC Continuing/Annual review approval/determination letter AND any other appropriate documentation from the IRB/EC. *(Refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual.)*

- A copy of the IRB/EC approved site-specific ICF(s) if revised at the time of Continuing/Annual review.

- A copy of the CRS's IRB/EC and other applicable RE/Regulatory Authority(ies) submission letter(s).

- A copy of all correspondence between the CRS and IRB/EC and other applicable RE/Regulatory Authority(ies).

NOTE: *All IRB/EC approval letters for Continuing/Annual review must state that the approval is for continuing review (i.e., similar terminology is acceptable: yearly review, annual review)*

NOTE: *Documentation of IRB/EC receipt of continuing review request alone does not satisfy the DHHS requirement regarding documentation of Continuing/Annual review and approval by the IRB/EC.*

NOTE: *The DAIDS PRO will not review any revised site-specific ICF(s) submitted with the continuing/annual review registration submission.*

CRSs will only be sent a Confirmation of Submission notice that indicates continuing/annual review materials have been received by the DAIDS PRO. CRSs will *NOT* receive any additional notifications from the DAIDS PRO for Continuing/Annual review documentation unless there is a problem with the documentation submitted (i.e., incomplete packet or inappropriate review by the IRB/EC). If problems are noted, the DAIDs PRO will follow-up via e-mail to inform the CRS about the deficiencies and to request corrected continuing/annual review documentation.

If a CRS's IRB/EC procedures for expedited review deviate from those as specified in OHRP guidance (i.e., specific pre-approved country procedures), then the CRS must provide documentation of the IRB/EC procedures to the DAIDS PRO at the same time the CRS submits their IRB/EC Continuing/Annual review approval documents. In addition, documentation of any change in timing of the IRB/EC review procedure for Continuing/Annual reviews for the CRS must be submitted to the DAIDS PRO along with the final IRB/EC Continuing/Annual review approval letter(s).

Lapses in Continuing Review

Per the DHHS regulations 45 CFR 46.103(b) and 46.109(e) and OHRP guidance on continuing review, if there is a lapse in continuing review (i.e., If an investigator has failed to provide continuing review information to their IRB/EC or the IRB/EC has not reviewed and approved a research study by the Continuing/Annual review date specified by the IRB/EC), the research at the CRS must stop, unless the IRB/EC finds that it is in the best interest of individual participants to continue participating in the research interventions or interaction. Enrollment of new participants cannot occur after the expiration of IRB/EC approval(s).

CRSs should contact their DAIDS Office for Clinical Site Oversite (OCSO) representative and/or DAIDS Program Officer when there is any lapse and for additional guidance and information.

CRSs should submit IRB/EC lapse documentation (i.e., the site's documentation of the lapse to the IRB/EC and the IRB/EC's response) to the DAIDS PRO.

7. Site Initiated Revisions to Site Informed Consent Forms (ICFs)

Modifications to a CRS's site-specific ICFs are considered site initiated when the changes are made as a result of new information or at the request of the IRB/EC and other applicable REs/ Regulatory Authority(ies).

Revisions to a CRS's site-specific ICFs are only considered site-initiated when revisions have been made after the CRS has received a Registration Notification from the DAIDS PRO for the most current DAIDS-approved protocol version. Any changes made to a CRS's ICF(s) prior to receiving a Registration Notification from the DAIDS will be considered part of the CRS's initial or amendment registration. For additional information on initial and amendment registration submissions refer to Initial Registration and Amendment Registrations of this manual.

Site-initiated revisions DO NOT affect the final DAIDS protocol version number and CRSs must be sure that the correct DAIDS protocol version number, remains on all site ICF(s). For version tracking purposes at the CRS, CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the final DAIDS protocol version number and/or final version date of the protocol document approved by DAIDS should remain on all site- specific ICFs as well.

The following documentation must be submitted to the DAIDS PRO for all site-initiated revised ICFs:

- A copy of the site-initiated revised ICF(s).
- A copy of the site's IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s) and any other appropriate documentation from the IRB/EC other RE/Regulatory Authority(ies). *Refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual for detailed information)*

NOTE: *If a site initiated revised ICF submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

Once the CRS receives approval from their IRB/EC and other applicable RE/ Regulatory Authority(ies), the CRS may implement the revised site-specific ICFs immediately (i.e. without delay, usually at the participant's next scheduled study visit). The DAIDS PRO will not review the site-initiated revisions to CRS's ICFs.

CRSs will be sent a Confirmation of Submission notice that indicates materials have been received by the DAIDS PRO. CRSs will NOT receive any additional notifications from the DAIDS PRO for site-initiated revisions to site-specific ICFs.

8. Updated Form FDA 1572 or DAIDS IOR Form

When there is **any** major change to the information listed on the Form FDA 1572/DAIDS IOR Form submitted to the DAIDS PRO, a CRS should submit an updated Form FDA 1572 (IND studies) or DAIDS IOR Form (Non-IND studies) to the DAIDS PRO within 15 calendar days.

The following documentation should be submitted to the DAIDS PRO for all Updated Form FDA 1572s/DAIDS IOR Forms -

- A copy of the updated Form FDA 1572 signed and dated by the IOR (for studies conducted under an IND), or
- A copy of the updated DAIDS IOR Form signed and dated by the IOR (for non- IND studies).

NOTE: *If there is a Change of IOR (listed in Section 1 of either form), refer to Change of Investigator of Record (IOR)" of this manual.*

NOTE: *CRSs should submit a copy of the signed and dated Form FDA 1572/DAIDS IOR Form to the DAIDS PRO and retain the original version in their regulatory files at the site.*

CRSs will be sent a Confirmation of Submission notice that indicates materials have been received by the DAIDS PRO. CRSs will NOT receive any additional notifications from the DAIDS PRO for updated Form FDA 1572s or DAIDS IOR Form unless the updated document(s) results in a Change of IOR at the CRS.

9. Deregistration

Any CRS that has completed the DAIDS protocol registration process for a protocol (main or sub-study), must complete the DAIDS deregistration process for each protocol to which it is registered.

NOTE: *Deregistration is NOT automatic when a study is completed.*

Deregistration can occur when:

- The CRS no longer has participants on study (all follow-up has been completed) and does not plan to enroll additional subjects.
- If no participants were ever enrolled at the CRS and the study has closed to accrual.

In addition, a CRS should check with their DAIDS Clinical Trials Network or DAIDS Program Officer to confirm if there are any protocol, network and/or DAIDS specific requirements prior to deregistering with the DAIDS PRO and/or closing/terminating the study with the IRB/EC.

The DAIDS deregistration process is independent of a CRS's closure/termination of a study at their IRB/EC. The IRB/EC's determination to close or terminate a study is *NOT* required for a CRS to deregister with DAIDS. Completion of the DAIDS deregistration process indicates that a CRS's participation in a study is complete but does not reflect the closure of a multi-center study at all CRSs participating in the study.

If a CRS plans to complete the DAIDS deregistration process for a study but will not be closing/terminating the study at their IRB/EC, the CRS should consult its IRB/EC to confirm any requirements and/or standard operating procedures that must be met prior to deregistration. A CRS's IRB/EC may require the continued submission of safety information and/or other data for the study. In this case, deregistration with DAIDS PRO should *NOT* be done until the study has been completed at all participating sites.

The following documentation must be submitted to the DAIDS PRO for all deregistration requests:

- Request stating that the CRS no longer intends to participate in the protocol(s), and/or
- A Copy of the IRB/EC closure/termination letter for the protocol if the protocol has been closed with the IRB/EC at the time of deregistration

A CRS will receive a Deregistration Notification from the DAIDS PRO when deregistration has been reviewed and approved by the DAIDS PRO.

NOTE: *A CRS is not considered deregistered until a Deregistration Notification has been issued by the DAIDS PRO.*

Once a CRS receives a Deregistration Notification for a protocol, the CRS is no longer required to submit any additional protocol registration documents to the DAIDS PRO if the protocol amends. A CRS must continue to follow their IRB/EC requirements for submission of documents if the protocol has not been closed/terminated with the IRB/EC.

Upon completion of the DAIDS deregistration process, a CRS will no longer receive safety information (i.e., safety reports, safety memos, investigator's brochures) from the DAIDS RSC Safety Information Center.

Additional guidance is available regarding the DAIDS registration process along with a summary of site responsibilities once deregistration is complete. This information is located on the DAIDS Deregistration Process Guidance under the "Protocol Registration" section.

VII. Definitions

Clinical Research - Research conducted on participants, material, or data of human origin with an identifiable person as the source. Clinical research includes exploratory, behavioral and observational studies. All clinical trials are a subset of clinical research. (DAIDS)

Clinical Research Site (CRS) - Distinct locations (i.e., hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) supported and/or sponsored by NIAID (DAIDS) where qualified professionals conduct clinical research in accordance with good clinical practice (GCP) and applicable regulations. (DAIDS)

Clinical Research Site (CRS) Leader - The onsite senior research scientist responsible for the administrative and scientific components of the CRS. The CRS leader is responsible for overall site activities, including day-to-day operations, performance, and compliance at the site level. (DAIDS)

Clinical Sciences Review Committee (CSRC) - The Division of AIDS internal scientific review committee responsible for the programmatic review of therapeutic protocols sponsored by DAIDS. The review will include careful assessment of the scientific objectives, design, safety, ethics, and feasibility of proposed research protocols. Scientific representatives from collaborating NIH Institutes and Centers participate as appropriate. (DAIDS)

Clinical Trial - A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. (NIAID).

Clinical Trial Applications (CTA): An Investigational New Drug Application for any Product filed with the FDA pursuant to Title 21 of the Code of Federal Regulations, Part 312 ("IND") or the submission to a competent Regulatory Authority within the EU of a request for an authorization concerning a clinical trial, as envisaged in Article 9, paragraph 2, of Directive 2001/20/EC, or any comparable filing made with a Regulatory Authority in another country or territory other than the U.S. or the EU.

Code of Federal Regulations (CFR) - Published by the U.S. Office of the Federal Register National Archives and Records Administration, these are detailed procedures for meeting requirements authorized by law:

> ***Title 21*** - Food and Drugs (covers regulations administered by FDA as authorized by the Food, Drug and Cosmetic Act).
>
> ***Title 45*** - Public Welfare (includes regulations administered by Office for Human Research Protections (OHRP) relating to the protection of human subjects). (DAIDS)

Curriculum Vitae (CV) - A statement of investigator's qualifications including professional experience accomplishments, educational background, and any publications. This document is required for all initial protocol registrations. (DAIDS)

Division of AIDS (DAIDS) - One of six divisions within the National Institute of Allergy and Infectious Diseases. DAIDS is responsible for the initiation, management, and oversight for the clinical trials and research that is sponsored and/or supported by NIAID (DAIDS). (DAIDS)

DAIDS Protocol Registration Office (PRO) - An office within the DAIDS Regulatory Support Contract (RSC) that receives and processes all protocol registration materials for DAIDS. (DAIDS)

DAIDS Protocol Registration System (DPRS) -An internet-based system that allows DAIDS Clinical Research Sites (CRS) to submit and track all documents submitted to the DAIDS Protocol Registration Office (PRO). (DAIDS)

DAIDS Regulatory Support Contract (RSC) - A contract that provides clinical, regulatory and technical support services for NIAID (DAIDS)-supported and/or - sponsored clinical trials. (DAIDS)

DAIDS-sponsored - DAIDS is responsible for the management (including submission of the Investigational New Drug Application (IND) and Investigational Device Exemption (IDE) Application to FDA, and initiation of the study) and oversight for the trial. (DAIDS)

DAIDS-supported - Clinical research activities would be considered to be supported by NIAID (DAIDS) under one or more of the following circumstances:

1. DAIDS provides direct funding to an institution via a grant, contract or cooperative agreement for the clinical research activities; or indirect funding via a subcontract executed under a DAIDS-supported award to another institution.

2. DAIDS provides other tangible support for the clinical research activities which includes, but is not limited to, regulatory support, site monitoring services, study product supply, management and distribution services.

3. DAIDS-supported central laboratory or data management center receives from other organizations specimens or data for processing or analysis and the results or analyses, will be used to direct involvement of participants in clinical research activities. (DAIDS)

Electronic Protocol Registration (EPR) - An alternate way CRSs can submit registration materials via e-mail to the DAIDS PRO if they encounter problems when trying to submit registration materials through the DPRS. (DAIDS)

European Medicines Agency (EMA) - A decentralized agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.

Food and Drug Administration (FDA) - A public health agency within the United States (U.S.) Department of Health and Human Services. FDA's mission is to promote and protect public health by helping safe and effective products reach the market in a timely way and monitoring products for continued safety after they are in use as authorized by The Federal Food, Drug and Cosmetic Act. (DAIDS)

Form FDA 1572 - FDA required document in which clinical investigators agree to conduct the clinical trials according to U.S. federal regulations. The Form FDA 1572 is signed, and a copy submitted to the IND sponsor. (DAIDS)

Full Version Protocol Amendment - Protocol modifications that result in a change in protocol version number. This new protocol version incorporates any currently proposed changes in addition to those made in all Clarification Memos (CMs) and Letter of Amendments (LOAs) that have been approved since the finalization of the previous protocol version. (DAIDS)

International Conference on Harmonisation (ICH) Guidelines
Developed, through a collaboration between the FDA and regulatory agencies in Japan and the European Union, to "harmonize" regulatory requirements to produce marketing applications acceptable to the United States, Japan, and the countries of the European Union. (DAIDS)

Institutional Biosafety Committee (IBC) - Committee set up by an institution under NIH guidelines to review recombinant DNA research and ensure its appropriate use. IBCs may also review other bio hazardous research, including select agents. (NIAID)

Institutional Review Board/Ethics Committee (IRB/EC) - Committee used by an institution to ensure the protection of human subjects by independently approving, modifying, or disapproving research protocols. (NIAID)

Investigational New Drug (IND) Application - A request for authorization from the FDA to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application. (FDA) An IND application is required by the FDA before clinical trials of an investigational drug or biological agent may be initiated. An IND is also generally required if the U.S. FDA has not approved the route of administration, dosage level, or patient population for the drug or biological agent. (DAIDS)

Investigator of Record (IOR) - The individual at the CRS responsible for ensuring that a clinical trial is conducted in accordance with the protocol, applicable U.S. federal regulations, in-country regulations and any provisions imposed by the reviewing IRB/EC/other regulatory entity. This person is the signatory for the Form FDA 1572 for studies conducted under an IND or the DAIDS Investigator of Record Form for non-IND studies.

Investigator of Record (IOR) Form - A document required by DAIDS for non-IND studies. By signing the document, the IOR accepts full responsibility for conduct of the trial at their CRS. (DAIDS)

Letter of Amendment (LOA) - A revision to a protocol made by the Protocol Team/Chair/Awardee through a letter that requires DAIDS final approval/sign-off before implementation. Changes described in a LOA are listed in a document that is separate from the protocol document itself and will NOT result in the change to the DAIDS protocol version number. (DAIDS)

National Institute of Allergy and Infectious Diseases (NIAID) - NIH institute that conducts and supports research to understand, treat, and prevent infectious, immunologic, and allergic diseases. (NIAID)

National Institutes of Health (NIH) - A Federal agency whose mission is to improve the health of the people of the United States. NIH is a part of the Public Health Service, which is part of the U.S. Department of Health and Human Services. (NIH)

Observational Study - A type of study in which individuals are observed or certain outcomes are measured, but no treatments or interventions are assigned by the study. (DAIDS)

Office for Human Research Protections (OHRP) - U.S. Department of Health and Human Services (DHHS) office overseeing human subject protection regulations for HHS-supported research. (NIH)

Office for Policy in Clinical Research Operations (OPCRO) - An office in DAIDS that provides a variety of clinical research management resources and oversight to the DAIDS clinical research portfolio. This includes overseeing the development, standardization, implementation and execution of policies, procedures and standards of conduct for all DAIDS domestic and international clinical research. (DAIDS)

Prevention Sciences Review Committee (PSRC) - The Division of AIDS internal scientific review committee responsible for the programmatic review of vaccine and prevention protocols sponsored by DAIDS. The review will include careful assessment of the scientific objectives, design, safety, ethics, and feasibility of proposed research protocols. Scientific representatives from collaborating NIH Institutes and Centers participate as appropriate. (DAIDS)

Protocol Registration Notifications - The following are notifications that a CRS may receive from the DAIDS PRO:

1. ***Confirmation of Submission*** - A notification sent out to the CRS Coordinator and IOR confirming that registration materials have been successfully submitted to the DAIDS PRO. If a CRS does not receive a Confirmation of Submission Notification within 24-48 hours of submitting registration documents to the DAIDS PRO, the CRS should contact the DAIDSPRO to find out how to proceed.

2. ***Registration Notification*** - A final notification from the DAIDS PRO indicating that a CRS has successfully completed the protocol registration process.

3. ***Registration with Required Corrections Notification*** -A notification from the DAIDS PRO indicating that a CRS must make required corrections and submit them to their IRB/EC for review and approval OR must submit justification for why the required correction will not be made within 120 calendar days of the date the Registration with Required Corrections Notification was issued. A Registration with Required Corrections Notification indicates that a CRS may begin using the site- specific informed consent forms (ICFs) after protocol activation by the appropriate Operations Center, Data Management/Statistical Center or DAIDS Program.

4. ***Disapproval Notification*** - A notification from the DAIDS PRO indicating that the site-specific informed consent forms (ICFs) do not include all the required basic and additional elements to comply with U.S. federal regulations and DAIDS policy. The Disapproval Notification will outline the deficiencies that must be revised/corrected before a final Registration Notification can be issued. All revised site-specific ICFs must be approved by the IRB/EC prior to submission to the DAIDS PRO. A disapproval notification is NOT a final notification since corrective materials must be resubmitted.

5. ***Deregistration Notification*** - A final notification from the DAIDS PRO indicating that a CRS is no longer registered to a study and all associated sub-studies.

6. ***Change of IOR Approval Notification*** - A final notification from the DAIDS PRO indicating that DAIDS has approved the change of IOR for a protocol at a CRS.

7. ***Requested Materials Notice*** - A message from the DAIDS PRO indicating that additional/corrected materials are required as a result of an incomplete or inaccurate submission to the DAIDS PRO.

A Materials Request Notification stops the registration review process until the requested materials have been received at the DAIDS PRO. (DAIDS)

Protocol Registration Team (PRT) - A team within OPCRO responsible for managing the Protocol Registration (PR) process, which includes oversight of the DAIDS PRO. (DAIDS)

Regulatory Entity (RE)/Regulatory Authority - Any entity/body that has the power to regulate which includes authorities that review submitted clinical data and those that conduct inspections. These are sometimes referred to as competent authorities. These are entities/bodies whose approval/authorization/acknowledgment of a clinical trial is required for conducting a clinical trial. Any organization whose approval is required prior to a CRS's participation in DAIDS funded and/or Sponsored Clinical Trial. Includes but not limited to approvals from state/national health systems and administrative bodies, drug agencies etc. (DAIDS adopted from ICH E6)

Sub-Investigator - Any member of the clinical research team designated and supervised by the CRS Leader/IOR of a protocol at a CRS to perform critical trial related procedures and/or to make important clinical trial-related decisions. (DAIDS)

Sub-Study - A sub-study asks a separate research question from the parent protocol and may or may not contribute to the parent protocol's objectives but uses all or a subset of study participants or specimens. A sub-study can be included as part of the main/parent protocol document or may not be included in the main protocol but requires current or previous participation in the main protocol. (NIAID)

The following are different types of sub-studies that a site may protocol register:

1. ***Embedded Sub-study*** - A sub-study that is part of a main protocol that may or may not have a separate ICF. Embedded sub-studies have the same protocol version number as the main study and have a separate protocol number and/or DAIDS protocol ID number. If there is a full version Amendment to the main study, when protocol registering to the amendment, sites are required to protocol register to all embedded sub-studies. A CRS will receive a registration notification for each embedded sub-study that is submitted for protocol registration. LOA registrations are only completed under the Main study however if the LOA requires revision to the sub-study IC, then the site IC should be submitted under the sub-study as a Site Revised IC.

2. ***Stand Alone Sub-study*** - A sub-study that is not part of the main protocol but requires participants to be enrolled in the main study or have previously participated in the main study. A stand-alone sub-study is an independent protocol that may or may not have the same protocol version number/date as the main study and will always have a separate protocol number and/or DAIDS protocol ID number. A CRS should submit all required documents (i.e. IRB/EC approval letter[s], site-specific informed consent form[s], Form FDA 1572 and/or DAIDS IOR Form, and IOR CV) when registering to a stand- alone sub-study. A CRS will receive a registration notification for each stand-alone sub-study that is submitted for protocol registration. (DAIDS). Amendment and LOA registrations should be submitted independently from the main study.

VIII. DAIDS Protocol Registration Office Contact Information and DPRS Access

The DAIDS Protocol Registration Office (PRO) has two different e-mail addresses - one for submission of protocol registration documents and a second for questions and general correspondence.

A. Contact Information for Questions and General Correspondence

E-mail: protocol@tech-res.com
Phone: 301-897-1707
Office Hours: Monday through Friday 8:30 AM to 5:00 PM (U.S. Eastern Standard Time)

Effective January 2012, all sites participating in NIAID (DAIDS)-supported and/or - sponsored clinical research that requires protocol registration, are required to submit protocol registration materials to the DAIDS PRO through the DAIDS Protocol Registration System (DPRS). Information on the DPRS and how to access the system is available on the DPRS website or information on how to submit protocol registration materials through the DPRS once a CRS has received a user name and password, refer to Appendix A of this manual.

In order to gain access to the DPRS, site personnel must complete the DPRS training that's available online at DAIDS Learning Portal.

First, log in to the DAIDS Learning Management System (LMS) with your user name and password. Then enter DPRS into the search field and select the DPRS training course. If you do not have a DAIDS LMS account, click to request account access.

At the time of completion of the DPRS training, a username and password will be provided to the person who completed the training. If DPRS login details have not been received, contact DAIDS-ES Support at CRMSSupport@niaid.nih.gov.

If a CRS encounters problem when submitting protocol registration materials through the DPRS, a CRS can submit protocol registration materials via e-mail to the DAIDS Electronic Protocol Registration (EPR) mailbox. If a CRS submits materials through the EPR mailbox, the e-mail message must outline the details of what is being submitted, and the kind of registration that is being submitted.

Information on protocol registration timelines is available on the DAIDS RSC Website under the "Protocol Registration" section.

B. Appendix A - Instructions on How to Access and Submit Protocol Registration Materials through the DAIDS Protocol Registration System (DPRS)

How do I gain access to DPRS?

1. DPRS Access

DPRS can be accessed via the DAIDS Learning Portal. DPRS Training completion is required to gain DPRS access. Log into the DAIDS Learning Management System (LMS) with your user name and password. Then enter DPRS into the search field and select the DPRS training course. If you do not have a DAIDS LMS account, click here to request account access.

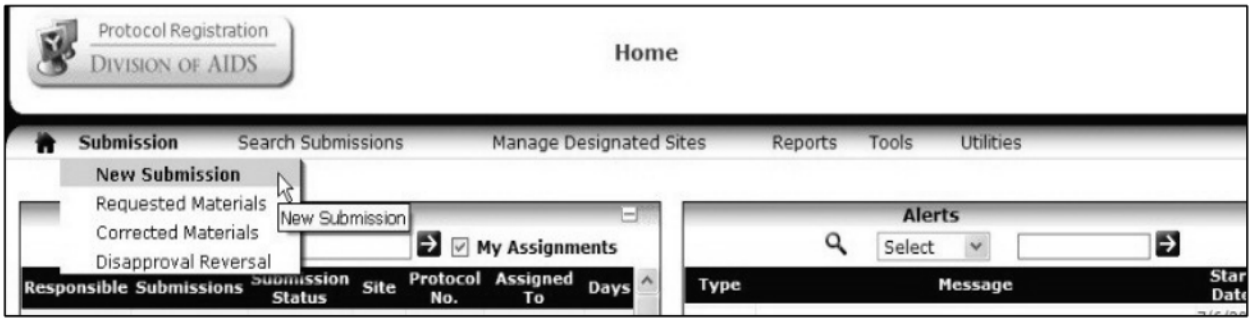
Once the DPRS training has been completed, DPRS user log-in and password will be sent to the trainee. If the training has been completed, but have not received DPRS login details yet, contact DAIDS-ES Support at CRMSSupport@niaid.nih.gov.

2. How do I access the New Submission screen?

Go to the DAIDS Protocol Registration Page. Enter your user name and password and click **Login**.

From the Home Page, click Submission on the main navigation bar and then click New Submission from the drop-down menu, which takes you to the New Submission page.

Figure 1: New Submission Option



3. How do I complete the Site Submission process?

Enter the Submission Details - Enter the appropriate information under the **Site and Protocol details** heading. Click the LOV icon to select the Site, IOR and Protocol No. Click the list of values to select the version/LOA.

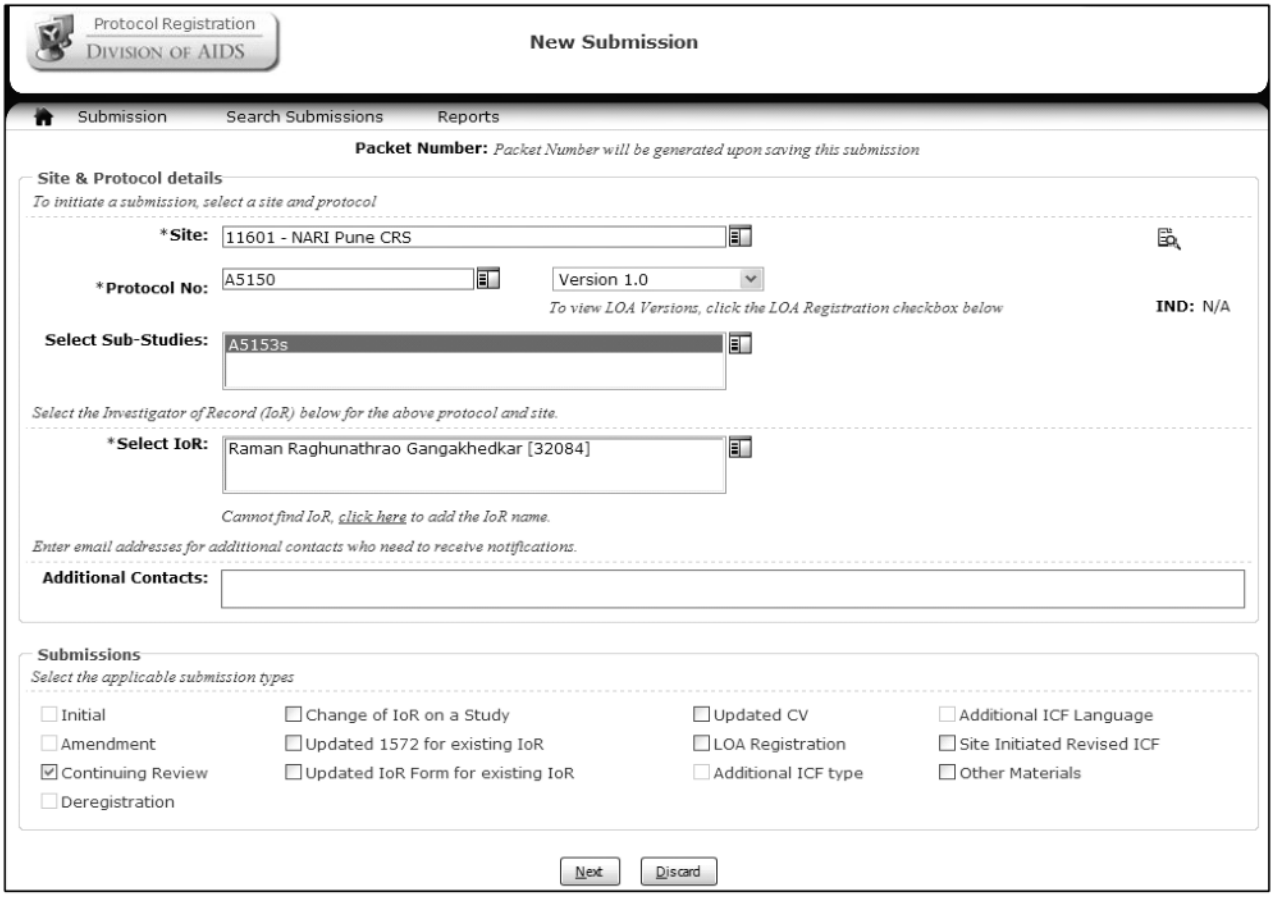
Select Sub-Studies - This list of values displays all embedded sub-studies associated with the study. Select a sub-study displayed to submit materials for the sub-study along with the study. The packet will be created when the main study is submitted.

Submissions - Select the appropriate checkboxes under the Submissions heading.

NOTE: *The system selects the same submission type for the sub-study as on the main study.*

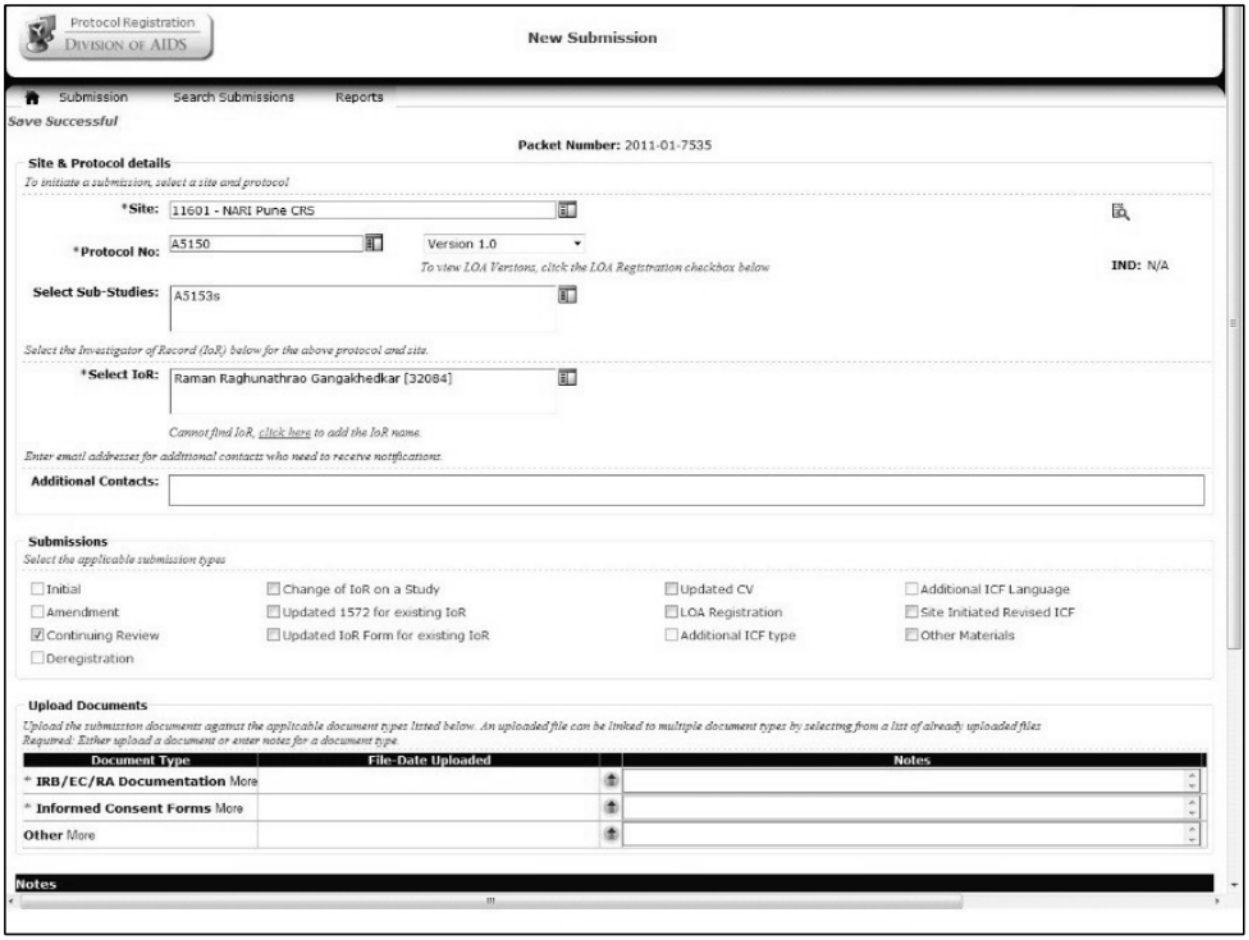
Next - Click **Next**. If the save is successful, the Upload Documents heading appears in the lower half of the screen.

Figure 2: Enter details in the New Submission screen.



Upload Documents - Click the upload icon to upload the appropriate documents. Enter notes to provide additional clarification. Click **Save**.

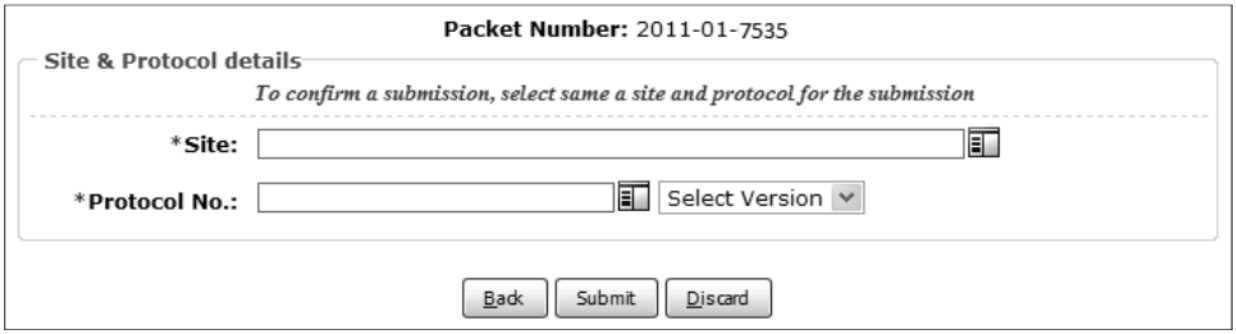
Figure 3: Upload documents in the New Submission screen and add notes.



Confirm Submission Details - When finished, click **Submit**. At the pop-up confirmation window, confirm the Site, IOR Name and Protocol No. Select the version and again click **Submit**.

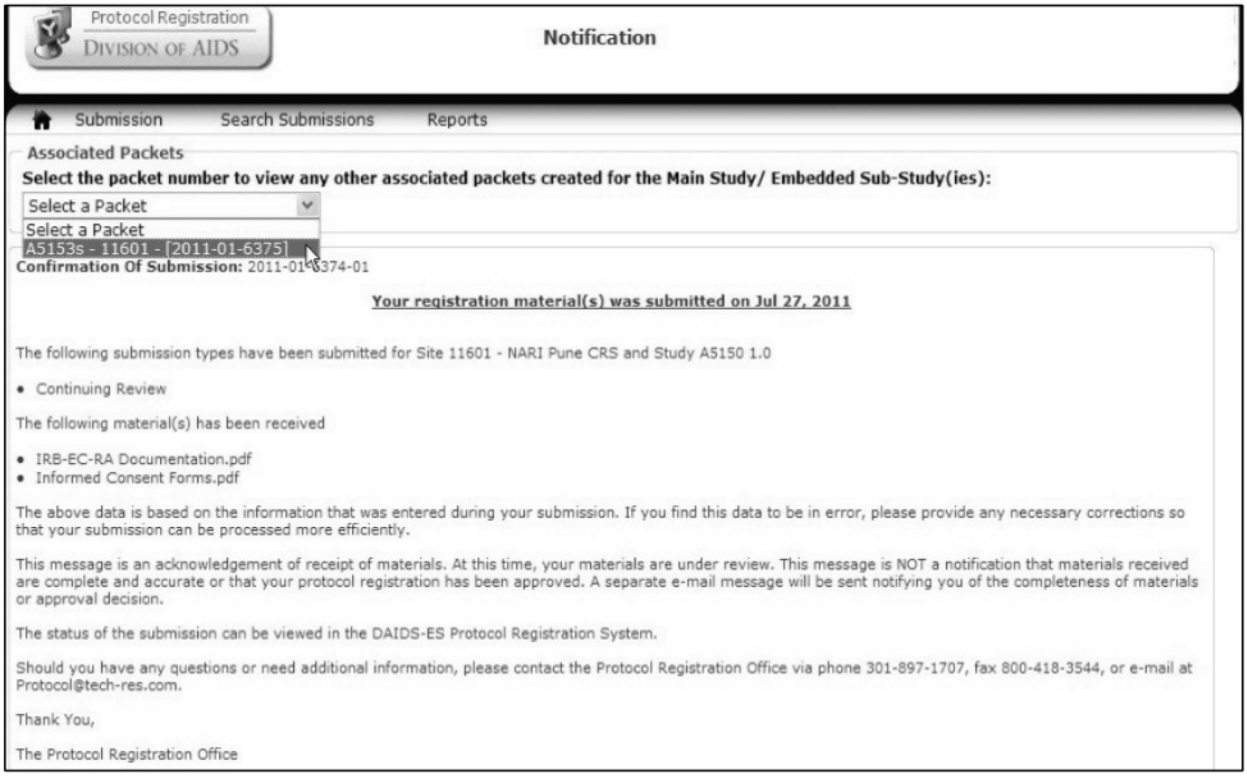
The system confirms whether the submission was successful.

Figure 4: Confirm Submission Details.



Optional - System will provide option to submit sub-study packets that have not yet been submitted by selecting a packet number at the top of the Notification screen.

Figure 5: Navigate to associated packets yet to be submitted.



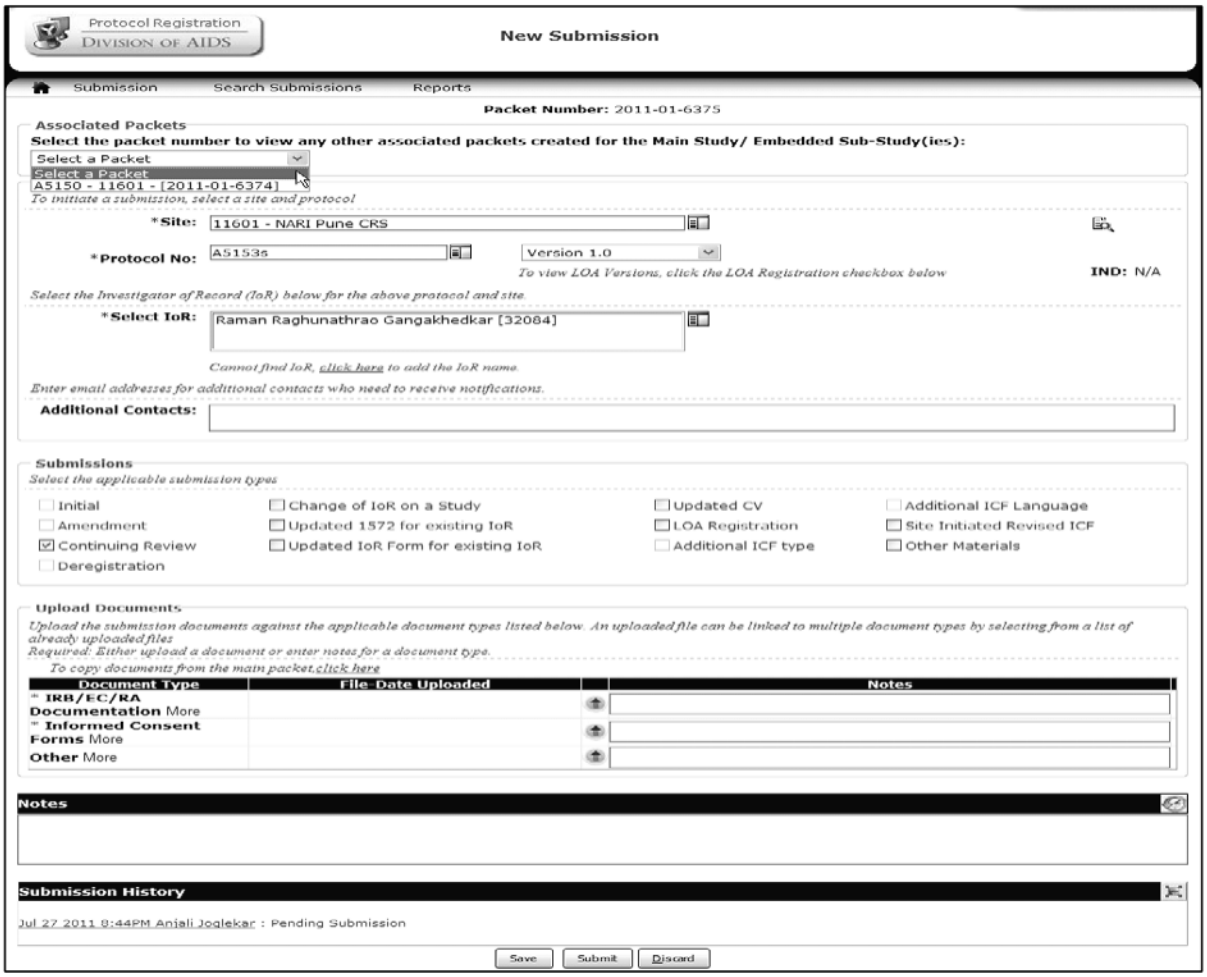
4. How do I view the sub-study packet?

Select a packet number at the top of the screen to view any other associated packets for this study. The Sub-Study screen appears similar to the main submission except the Protocol Number is changed to the sub-study number. The submission type remains the same.

NOTE: *You can use this feature to toggle between the sub-study packets. You also can copy person information to sub- study packets.*

Click the Upload Documents hyperlink in the associated packets to copy documents from the main packet.

Figure 6: Viewing the sub-study packet.



5. Still Have Questions?

E-mail: CRMSSupport@niaid.nih.gov

Phone: 1-240-778-2517

IX. DAIDS Protocol Registration Revision History and Approval

MAN-A15-OPC-001.00 is the initial version of the DAIDS Protocol Registration manual submitted to the DAIDS Quality Management System (QMS) as version 00. Refer to section II. for a detailed list of updates for this version.

There were four previous versions of the DAIDS Protocol Registration Manual, August 2004, March 2010, May 2012, and April 2015 published on the DAIDS Clinical Research Policies webpage prior to the implementation of the DAIDS QMS in 2018

Printed Name/Title	Signature	Date

1.0 PURPOSE

This document states the requirements for the publication, presentation, and disclosure of any work conducted by the AIDS Clinical Trials Group (ACTG) Network, or governed by subcontract agreements executed by Partners HealthCare (PHS) on behalf of the ACTG.

2.0 SCOPE

This SOP applies to all ACTG-related publications including manuscripts, abstracts, Executive Summaries, Clinical Trials Unit (CTU)/Clinical Research Site (CRS) Scientific and Participant Summaries, and press releases.

It is the policy of the ACTG to publish and share research results in a timely manner in accordance with the NIH Public Access Policy http://publicaccess.nih.gov/policy.htm. It is also the policy of the ACTG to publish the results of the main study/project primary manuscript prior to those of substudies and secondary manuscripts, unless otherwise approved by the Scientific Agenda Steering Committee (SASC). This policy is expected to be followed for ACTG studies, collaborative studies with cosponsoring agencies or other clinical trials networks, and studies in which data are collected and analyzed by a network or group other than the ACTG Statistical and Data Management Center (SDMC), unless alternative policies are mutually agreed upon and codified in the Clinical Trials Agreement (CTA), Letter of Understanding (LOU), or Memorandum of Understanding (MOU), or otherwise approved by the ACTG Executive Committee (AEC).

Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), or the AEC, with DAIDS/NIAID approval, have authority to embargo any/all information in Executive Summaries and accompanying documents, CTU/CRS Scientific Summaries, Participant Summaries, and press releases, until information is made public (i.e., abstract presentation or manuscript publication).

3.0 DEFINITIONS

3.1 **Writing Team**—A subgroup of the protocol team members who collaborate to write an abstract or manuscript summarizing results of the study protocol. Under certain circumstances, specialists who are not protocol team members may be included.

3.2 **Masthead authors**— The group that is listed as authors on the manuscript or abstract.

3.3 **Scientific Committee (SC)** —Committee responsible for reviewing manuscript or abstract prior to journal or conference submission, includes Transformative Scientific Groups (TSGs), Collaborative Science Groups (CSGs) and SASC.

3.4 **Designated committee reviewer**—Committee member assigned to review manuscript or abstract prior to journal or conference submission if Scientific Committee chair and vice chair have conflicts.

3.5 **Primary manuscript**—Manuscript that reports data and results of primary objectives of a trial.

3.6 **Secondary manuscript**—Manuscript that reports secondary analysis results or objectives of a trial, or scientific questions outside the primary objectives, e.g., baseline data reports, secondary objectives specified in the protocol, cross-protocol data, or analysis of specimens collected as part of a trial, but used for analyses not previously specified in the primary protocol.

3.7 **New Work Concept Sheet (NWCS)**—Study that reports results of analysis of specimens from an existing ACTG protocol that is not specified in an ACTG protocol or defined as a secondary analysis within 60 days of receipt of the final analysis by the writing committee chair. (See SOP ACTG-109, NWCS Development and Review)

3.8 **Data Analysis Concept Sheet (DACS)**—Study that reports results of analysis of data from an existing ACTG protocol(s) that were not specified in the ACTG protocol or defined as a secondary analysis for that ACTG protocol within 60 days after receipt of the final analysis by the writing committee chair. (See SOP ACTG-106, DACS Development and Review)

3.9 **Non-Protocol related abstract or manuscript**—An abstract or manuscript that is not affiliated to an ACTG protocol that contains ACTG-related data (e.g. related to committee, site or laboratory, ACTG policies, process, or procedure-related).

3.10 **Abstract**—Brief report of ACTG-related data, prepared for submission to a conference. May be classified as a regular abstract or a late-breaker abstract.

3.11 **Protocol team**—Group of team members that appear in the protocol roster, which usually includes pharmaceutical/industry representatives and other funders of the study.

3.12 **Executive Summary**—Summary of ACTG study results of the primary objectives of a trial; disseminated prior to public presentation or publication of the results.

3.13 **CTU/CRS Scientific Summary**—Limited scientific summary of the study results; disseminated to ACTG CTUs and CRSs prior to public presentation or publication of the results, if a full Executive Summary is not warranted.

3.14 **Participant Summary**—Summary for study participants describing the study results and implications of them. To be distributed with Executive Summary or CTU/CRS Scientific Summary.

3.15 **National Institutes of Health Manuscript Submission System (NIHMS)**—An online system for submitting and managing final, peer-reviewed manuscripts in accordance with the NIH Public Access Policy.

3.16 **PubMed Central (PMC)**—The National Institute of Health (NIH) digital archive of full-text, peer-reviewed journal articles; its content is publicly accessible and integrated with other databases (see: http://www.pubmedcentral.nih.gov/).

3.17 **Publication costs**—The author fees associated with publishing peer-reviewed manuscripts.

3.18 **Primary Completion Date**—The date on which the last participant in a clinical study was examined or received an intervention and that data for the primary outcome measure were collected.

4.0 RESPONSIBILITIES AND PROCEDURES

4.1 ACTG Manuscripts

Primary Manuscripts

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Formation of writing team	~ 15 weeks prior to closed to follow-up date/primary completion date	• Form writing team • Notify ACTG Publications Office and committee leadership of writing team members (see *Appendix 1: Writing Team Guidelines*). • Review writing team membership; if necessary make recommendations	Protocol Core Team Protocol Chair/Writing Chair and/or CTS SC Chair/Committee Leadership
Preparation of data analysis plan	12 weeks prior to closed to follow-up date/primary completion date.	• Define analysis plan prior to initiation of final data analysis. (See SOP ACTG-101) ○ Analyses using non-Statistical and Data Analysis Center (SDAC) statistical expertise must follow SOP ACTG -141 for the procedure for conduct of secondary analyses when SDAC resources are not available.	Writing Team
Determination of summaries	Near finalization of data analysis plan	• Determine a need for Executive Summaries and/or CTU/CRS Scientific Summaries based on primary analysis plan, or a preliminary analysis prior to preparation of full primary analysis report (see table for Executive Summary and/or CTU/CRS Scientific Summaries).	SC Chair, in consultation with DAIDS, SASC, protocol Chair, and statistician
Receipt of final primary analysis by protocol chair	5 months post closed to follow-up date (may be accelerated under select circumstances upon team agreement. SC and SDAC agreement is required in select cases).	• Send final analysis to protocol chair • Notify ACTG Publications Office that analysis has been sent	Protocol statistician Writing Chair, statistician, and/or CTS

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
60-Day preparation of manuscript	Upon receipt of primary analysis	• Oversee timely completion of manuscript and adherence to timelines	Committee Leadership/Writing Chair
		• Ensure that the journal's requirements are read and understood prior to any submission of a manuscript. If there are questions regarding special requirements/situations that are unfamiliar, the writing chair should consult with the ACTG Publications Office prior to submission of the manuscript. Questions regarding author's rights should be directed to the author's institution.	Writing Chair
		• Determine number and order of masthead authors; acknowledge ACTG support in the manuscript. When possible, journals should be chosen that do not limit the number of authors in the masthead. (See *Appendix 1: Writing Team Guidelines and Acknowledgements section*)	Writing Team
		• Contact ACTG Publications Office to solicit names and grant numbers of participating sites	Writing Chair
		• Finalize manuscript within 60 days from date final analysis is received by protocol chair.	Writing Team
30- Day Team Review of manuscript by masthead authors, writing team, and protocol team to include DAIDS, SDAC, and the pharmaceutical and biomedical representatives	Following 60-day writing period	• Send manuscript for 14-day review and sign-off (see *Appendix 3* for 14-day review distribution list). Pharmaceutical and biomedical industry representatives are allowed up to 30 days for review, unless otherwise specified in the CTA[2]. *NOTE: It is the Writing team's responsibility to ensure that all of the pharmaceutical/industry reps have been allowed adequate time to review the manuscript.* • If not already addressed in the Clinical Trials Agreement, request that the pharmaceutical company provide a statement indicating their willingness to share the study's protocol with the public at the journal's request.	Writing Chair

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Completion of final analysis report	Within 90-days after final primary analysis is received	• Send final analysis report with relevant additions to ACTG Network principal investigator (PI)/chair and vice chair, SC chair and vice chair ○ If additional analyses necessary for completion of the final analysis report will delay submission of the manuscript for ACTG review, an extension request should be submitted (see *Appendix 2*)	Protocol statisticians
Submission of manuscript for ACTG review following team review	90 days after final analysis is received by protocol chair	• Submit final draft to ACTG Publications Office, via Submission Central on the ACTG member website https://member.actgnetwork.org/pub/cs/review, after final team review. ○ If submitting to an Open Access journal, notify the ACTG Publications Office for determination of Open Access fee coverage (see Appendix 6 for more information).	Writing Chair
ACTG review of manuscript	10 business days	• Send final draft to SC chair/vice chair/designated committee reviewer for approval/disapproval • Send final draft to additional review parties for review concurrent with committee review (See *Appendix 3* for ACTG Publications Office manuscript review distribution list) [2] • Acquire a list of team members with significant financial interests, or a statement that none of them do, from the ACTG Financial Disclosure Coordinator (FDC). • Review manuscript and submit any comments to ACTG Publications Office[2].	ACTG Publications Office Financial Disclosure Coordinator Additional review parties
Completion of ACTG review	Within 10 business days after final draft is disseminated	• Review manuscript and return manuscript endorsement sheet to ACTG Publications Office (see *Appendix 4* for Committee Reviewer Responsibilities). • Send endorsement response and additional review party comments to corresponding author • Respond to review comments (via options below)	SC Chair/Vice-Chair/designated reviewer ACTG Publications Office Writing Chair

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		○ Approved [and reviewer does not want to see MS again]: proceed with submission to journal ○ Approved and reviewer wants to see manuscript again prior to submission: incorporate comments and send revised manuscript and responses to ACTG Publications Office within 20 days. ○ Disapproved: resubmit revised manuscript to ACTG Publications Office within 60 days for 10 day ACTG Review as indicated above. Note: Substantial changes following ACTG review must be agreed on by authors and SC chair/vice chair/designated committee reviewer. If agreement cannot be reached, refer to the SASC chair for resolution.	
Revision and resubmission of manuscript 60 days after acceptance with revisions or rejection	Within 60 days of rejection following initial ACTG review	• Distribute revised manuscript, review comments, and responses to writing team, masthead authors, and protocol team to include SDAC, DAIDS, and the pharmaceutical representatives for a 2nd team review ○ For NWCS and DACS, please resubmit to the team review parties outlined in Appendix 3. • Resubmit revised manuscript to ACTG Publications Office, via Submission Central on the ACTG member website, for a second ACTG review prior to journal submission. ○ Failure to submit for a 2nd ACTG review within 60 days may result in sanctions, as described in *Appendix 5: Sanctions*. • Send manuscript for 2nd 10-day ACTG review to SC Chair/Vice-Chair/designated reviewer • Respond to 2nd review comments via options listed in "Completion of ACTG Review" section above	Writing Chair Writing Chair ACTG Publications Office Writing Chair
Submission to journal	Within 30 days after ACTG approval	• Ensure authors' disclosure of potential conflicts of interest as required by journal policy.	Writing chair

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		• Prior to signing the journal publication agreement (or similar copyright transfer agreement)- ○ Ensure the publishing agreement allows the paper to be posted to PubMed Central, in accordance with NIH Public Access Policy. ○ Contact the ACTG Publications Office for assistance in retaining author rights for compliance to Public Access Policy. • At the time of journal submission, the journal must be notified that the manuscript was funded wholly or in part by NIH. • If a journal requests a statement about access to data, use the following statement: "Study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group." • If a journal requests at statement about access to data and statistical analysis programs, use the following statement: "Study data and statistical programming code are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group. • Submit journal review updates and decisions to ACTG Publications Office within 10 days after receipt. • Maintain copies of journal review comments (to be made available to SASC or SC upon request).	
Journal acceptance for publication	Following notification of acceptance for publication	• Awardees are responsible for ensuring manuscripts are submitted to the National Institutes of Health Manuscript Submission site (NIHMS) upon acceptance for publication. If the manuscript is being published in a journal that does not deposit final published articles in PubMed Central, the author is responsible for submission. The ACTG Publications Office at the Leadership and Operations Center can be contacted for assistance at ACTGPublications@partners.org or designated the submitter of the manuscript if the author is unable. • Approve the release and PubMed Central formatting of your manuscript when receiving the email notification from NIHMS[3]	Writing Chair or senior author

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		• If the authors are responsible for publication fees, see *Appendix 6: ACTG Publication Costs.*	
Assignment of scientific contribution credit	Within 30 days after publication	• Obtain an electronic copy of the published manuscript and, if appropriate, assign scientific contribution credit for the annual site and laboratory performance evaluations in accordance with SOP ACTG-126, respectively.	Network Coordinating Center
Referencing ACTG published manuscripts	Following publication of manuscript online or in journal	• When submitting an application, proposal, or report to the NIH, the PubMed Central reference number (PMCID) must be included when citing ACTG papers that arise from NIH-funded research.	ACTG members

Baseline and Secondary Manuscripts

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Formation of the writing team	May vary	• Form writing team • Notify ACTG Publications Office and committee leadership of writing team members (see *Appendix 1: Writing Team Guidelines*). • Review writing team membership; if necessary make recommendations	Protocol Core Team Protocol Chair/Writing Chair and/or CTS SC Chair/Committee Leadership
Preparation of data analysis plan	May vary	• Define analysis plan prior to initiation of final data analysis. (See SOP ACTG-101) ○ Analyses using non-Statistical and Data Analysis Center (SDAC) statistical expertise must follow SOP ACTG-158 for the procedure for conduct of secondary analyses when SDAC resources are not available.	Writing Team
Receipt of final analysis by protocol chair	May vary secondary to assays/texts completion	• Send final analysis to protocol chair • Notify ACTG Publications Office that analysis has been sent	Protocol statistician Writing Chair, statistician, and/or CTS

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
60-Day preparation of manuscript	Upon receipt of baseline or secondary analysis	• Oversee timely completion of manuscript and adherence to timelines	Committee Leadership/Writing Chair
		• Ensure that the journal's requirements are read and understood prior to any submission of a manuscript. If there are questions regarding special requirements/situations that are unfamiliar, the writing chair should consult with the ACTG Publications Office prior to submission of the manuscript. Questions regarding author's rights should be directed to the author's institution.	Writing Chair
		• Determine number and order of masthead authors; acknowledge ACTG support in the manuscript. When possible, journals should be chosen that do not limit the number of authors in the masthead. (See *Appendix 1: Writing Team Guidelines and Acknowledgements section*)	Writing Team
		• Contact ACTG Publications Office to solicit names and grant numbers of participating sites (only for major secondary manuscripts)	Writing Chair
		• Finalize manuscript within 60 days from date final analysis is received by protocol chair.	Writing Team

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
30-day team review of manuscript by masthead authors, writing team, and protocol team to include DAIDS, SDAC, and the pharmaceutical and biomedical representatives	Following 60-day writing period	• Send manuscript for 14-day review and sign-off (see *Appendix 3* for 14-day review distribution list). Pharmaceutical and biomedical industry representatives are allowed up to 30 days for review, unless otherwise specified in the CTA[2]. *NOTE: It is the Writing team's responsibility to ensure that all of the pharmaceutical/industry reps have been allowed adequate time to review the manuscript.* • If not already addressed in the CTA, request that the pharmaceutical company provide a statement indicating their willingness to share the study's protocol with the public at the journal's request.	Writing chair
Completion of final analysis report	Within 90-days after final analysis is received	• Send final analysis report with relevant additions to ACTG Network principal investigator (PI)/chair and vice chair, SC chair and vice chair • If additional analyses necessary for completion of the final analysis report will delay submission of the manuscript for ACTG review, an extension request should be submitted (see *Appendix 2*)	Protocol statisticians
Submission of manuscript for ACTG review following team review	90 days after final analysis is received by protocol chair	• Submit final draft to ACTG Publications Office, via Submission Central on the ACTG member website https://member.actgnetwork.org/pub/cs/review, after final team review. • If submitting to an Open Access journal, notify the ACTG Publications Office for determination of Open Access fee coverage (see Appendix 6 for more information).	Writing Chair
ACTG review of manuscript	10 business days	• Send final draft to SC chair/vice chair/designated committee reviewer for approval/disapproval • Send final draft to additional review parties for review concurrent with committee review (See *Appendix 3* for ACTG Publications Office manuscript review distribution list)[2] • Acquire a list of team members with significant financial interests, or a statement that none of them do, from the ACTG	ACTG Publications Office Financial Disclosure Coordinator

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		Financial Disclosure Coordinator (FDC). • Review manuscript and submit any comments to ACTG Publications Office[2].	 Additional review parties
Completion of ACTG review	Within 10 business days after final draft is disseminated	• Review manuscript and return manuscript endorsement sheet to ACTG Publications Office (see *Appendix 4* for Committee Reviewer Responsibilities). • Send endorsement response and additional review party comments to corresponding author • Respond to review comments (via options below) ○ Approved [and reviewer does not want to see MS again]: proceed with submission to journal ○ Approved and reviewer wants to see manuscript again prior to submission: incorporate comments and send revised manuscript and responses to ACTG Publications Office within 20 days. ○ Disapproved: resubmit revised manuscript* to ACTG Publications Office within 60 days for 10 day ACTG Review as indicated above. Note: Substantial changes following ACTG review must be agreed on by authors and SC chair/vice chair/designated committee reviewer. If agreement cannot be reached, refer to the SASC chair for resolution.	SC Chair/Vice-Chair/designated reviewer ACTG Publications Office Writing Chair
Revision and resubmission of manuscript 60 days after acceptance with revisions or rejection	Within 60 days of rejection following initial ACTG review	• Distribute revised manuscript, review comments, and responses to writing team, masthead authors, and protocol team to include SDAC, DAIDS, and the pharmaceutical representatives for a 2nd team review ○ For NWCS and DACS, please resubmit to the team review parties outlined in Appendix 3.	Writing Chair

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		• Resubmit revised manuscript to ACTG Publications Office, via Submission Central on the ACTG member website, for a second ACTG review prior to journal submission. o Failure to submit for a 2nd ACTG review within 60 days may result in sanctions, as described in *Appendix 5: Sanctions*. • Send manuscript for 2nd 10-day ACTG review to SC Chair/Vice-Chair/designated reviewer • Respond to 2nd review comments via options listed in "Completion of ACTG review" section above	Writing Chair ACTG Publications Office Writing Chair
Submission to journal	Within 30 days after ACTG approval	• Ensure authors' disclosure of potential conflicts of interest as required by journal policy. • Prior to signing the journal publication agreement (or similar copyright transfer agreement)- o Ensure the publishing agreement allows the paper to be posted to PubMed Central, in accordance with NIH Public Access Policy. o Contact the ACTG Publications Office for assistance in retaining author rights for compliance to Public Access Policy. • If a journal requests a statement about access to data, use the following statement: "Study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group. • If a journal requests at statement about access to data and statistical analysis programs, use the following statement: "Study data and statistical programming code are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group. • At the time of journal submission, the journal must be notified that the manuscript was funded wholly or in part by NIH.	Writing Chair

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		• Submit journal review updates and decisions to ACTG Publications Office within 10 days after receipt. • Maintain copies of journal review comments (to be made available to SASC or SC upon request).	
Journal acceptance for publication	Following notification of acceptance for publication	• If the manuscript is being published in a journal that does not deposit final published articles in PubMed Central, submit a request with the final peer reviewed version (e.g. Microsoft Word document), all tables, figures, and supplementary information, and a copy of the signed publication agreement (or similar copyright transfer agreement) to PubMed Central via NIHMS. The ACTG Leadership and Operations Center at ACTGPublications@partners.org can be contacted with questions. The Leadership and Operations Center can submit the manuscript on behalf of the corresponding author as a last resort. • Approve the release and PubMed Central formatting of your manuscript when receiving the email notification from NIHMS.[3] NOTE: If the authors are responsible for publication fees, see *Appendix 6: ACTG Publication Costs.*	Writing Chair or senior author
Assignment of scientific contribution credit	Within 30 days after publication	Obtain an electronic copy of the published manuscript and, if appropriate, assign scientific contribution credit for the annual site and laboratory performance evaluations in accordance with SOP ACTG-126, respectively.	Network Coordinating Center
Referencing ACTG published manuscripts	Following publication of manuscript online or in journal	When submitting an application, proposal, or report to the NIH, the PubMed Central reference number (PMCID) must be included when citing ACTG papers that arise from NIH-funded research.	ACTG members

NWCS/DACS Manuscripts

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
NWCS/DACS request for use of study data for NWCS or DACS Based on availability of data for use by investigators outside the protocol team through the submission and approval of a data request, for DACS and NWCS	One year after publication of primary manuscript and team confirmation of secondary analyses to be completed and published by the team	• Once the study data are openly available for use by investigators outside the protocol team, circulate NWCS and/or DACS as a courtesy to the primary protocol team, and if samples are to be used, ascertain whether or not sufficient samples are available for proposed work.	Protocol/Non-protocol investigators
Receipt of final analysis by protocol chair/lead investigator	May vary	• Send final analysis to protocol chair/lead investigator • Notify ACTG Publications Office that analysis has been sent	Protocol statistician Writing Chair, and/or statistician
60 –day preparation of manuscript	Upon receipt of analysis	• Oversee timely completion of manuscript and adherence to timelines • Determine number and order of masthead authors; acknowledge ACTG support in the manuscript. (See *Appendix 1: Writing Team Guidelines and Acknowledgements section*) • Finalize manuscript within 60 days from date final analysis is received by protocol chair.	Committee Leadership/Writing Chair Writing Team Writing Chair
30-day team review by masthead authors to include SDAC, the protocol chairs and pharmaceutical/biomedical industry representatives of the parent protocols	Following 60-day writing period	• Send manuscript for 14-day review and sign-off (see *Appendix 3* for 14-day review distribution list). Pharmaceutical, biomedical industry, or external collaborators are allowed up to 30 days for review, unless otherwise specified in the CTA[2]. *NOTE: It is the Writing team's responsibility to ensure that all of the pharmaceutical/industry reps have been allowed adequate time to review the manuscript.*	Writing Chair
Completion of final analysis report	Within 90-days after analysis received	• Send final analysis report with relevant additions to ACTG Network principal investigator (PI)/chair and vice chair, SC	Protocol statisticians

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		chair and vice chair ○ If additional analyses necessary for completion of the final analysis report will delay submission of the manuscript for ACTG review, an extension request should be submitted (see *Appendix 2*)	
Submission of manuscript for ACTG review following team review	90 days after final analysis is received by protocol chair	• Submit final draft to ACTG Publications Office, via Submission Central on the ACTG member website https://member.actgnetwork.org/pub/cs/review, after final team review. • If submitting to an Open Access journal, notify the ACTG Publications Office for determination of Open Access fee coverage (see Appendix 6 for more information).	Writing Chair
ACTG review of manuscript	10 business days	• Send final draft to SC chair/vice chair/designated committee reviewer for approval/disapproval • Send final draft to additional review parties for review concurrent with committee review (See *Appendix 3* for ACTG Publications Office manuscript review distribution list) [2] • Acquire a list of team members with significant financial interests, or a statement that none of them do, from the ACTG Financial Disclosure Coordinator (FDC). • Review manuscript and submit any comments to Publications Office[2].	ACTG Publications Office Financial Disclosure Coordinator Additional review parties
Completion of ACTG review	Within 10 business days after final draft is disseminated	• Review manuscript and return manuscript endorsement sheet to Publications Office (see *Appendix 4* for Committee Reviewer Responsibilities). • Send endorsement response and additional review party comments to corresponding author • Respond to review comments (via options below)	SC Chair/Vice-Chair/designated reviewer ACTG Publications Office Writing Chair

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		○ Approved [and reviewer does not want to see MS again]: proceed with submission to journal ○ Approved and reviewer wants to see manuscript again prior to submission: incorporate comments and send revised manuscript and responses to ACTG Publications Office within 20 days. ○ Disapproved: resubmit revised manuscript to ACTG Publications Office within 60 days for 10 day ACTG review as indicated above. Note: Substantial changes following ACTG review must be agreed on by authors and SC chair/vice chair/designated committee reviewer. If agreement cannot be reached, refer to the SASC chair for resolution.	
Revision and resubmission of manuscript 60 days after acceptance with revisions or rejection	Within 60 days of rejection following initial ACTG review	• Distribute revised manuscript, review comments, and responses to writing team, masthead authors, and protocol team to include SDAC, DAIDS, and the pharmaceutical representatives for a 2nd team review ○ For NWCS and DACS, please resubmit to the team review parties outlined in Appendix 3. • Resubmit revised manuscript to ACTG Publications Office, via Submission Central on the ACTG member website, for a second ACTG review prior to journal submission. ○ Failure to submit for a 2nd ACTG Review within 60 days may result in sanctions, as described in *Appendix 5: Sanctions*. • Send manuscript for 2nd 10-day ACTG review to SC Chair/Vice-Chair/designated reviewer • Respond to 2nd review comments via options listed in “Completion of ACTG review” section above	Writing Chair Writing Chair ACTG Publications Office Writing Chair

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Submission to journal	Within 30 days after ACTG approval	• Ensure authors' disclosure of potential conflicts of interest as required by journal policy. • Prior to signing the journal publication agreement (or similar copyright transfer agreement)- ○ Ensure the publishing agreement allows the paper to be posted to PubMed Central, in accordance with NIH Public Access Policy. ○ Contact the ACTG Publications Office for assistance in retaining author rights for compliance to Public Access Policy. • If a journal requests a statement about access to data, use the following statement: "Study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group." • If a journal requests at statement about access to data and statistical analysis programs, use the following statement: "Study data and statistical programming code are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group." • At the time of journal submission, the journal must be notified that the manuscript was funded wholly or in part by NIH. • Submit journal review updates and decisions to ACTG Publications Office within 10 days after receipt. • Maintain copies of journal review comments (to be made available to SASC or SC upon request).	Writing Chair
Journal acceptance for publication	Following notification of acceptance for publication	• If the manuscript is being published in a journal that does not deposit final published articles in PubMed Central, submit a request with the final peer reviewed version (e.g. Microsoft Word document), all tables, figures, and supplementary information, and a copy of the signed publication agreement (or similar copyright transfer agreement) to PubMed Central via NIHMS. The ACTG Leadership and Operations Center at ACTGPublications@partners.org can be contacted with questions. The Leadership and Operations Center can submit	Writing Chair or senior author

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		the manuscript on behalf of the corresponding author as a last resort. • Approve the release and PubMed Central formatting of your manuscript when receiving the email notification from NIHMS[3] • If the authors are responsible for publication fees, see *Appendix 6: ACTG Publication Costs.*	
Assignment of scientific contribution credit	Within 30 days after publication	Obtain an electronic copy of the published manuscript and, if appropriate, assign scientific contribution credit for the annual site and laboratory performance evaluations in accordance with SOP ACTG-126, respectively.	Network Coordinating Center
Referencing ACTG published manuscripts	Following publication of manuscript online or in journal	When submitting an application, proposal, or report to the NIH, the PubMed Central reference number (PMCID) must be included when citing ACTG papers that arise from NIH-funded research.	ACTG members

[1] *Timeline modified if study closes prematurely*
[2] *Timelines codified in CTA may supersede timelines set in this SOP.*
[3] *Please refer to http://publicaccess.nih.gov/FAQ.htm for an informative list of frequently asked questions.*

4.2 ACTG Abstracts

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Team review of abstract	Prior to submission for ACTG review	• For main protocol or substudy abstracts, submit a request for team review to the writing team, masthead authors, and the protocol team, to include all current members including SDAC[4], DAIDS[4], the protocol chairs, and the pharmaceutical and biomedical industry representatives[3] (if applicable) o For substudies, the main study team and substudy team must be included • For NWCS and DACS abstracts, submit a request for team review to the masthead authors to include SDAC if SDAC[2] is a co-author, the protocol chair(s) of the parent protocol(s), and	Writing Chair

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		the pharmaceutical and biomedical industry representatives of the parent protocol(s) The ACTG Publications Office can be contacted for this information.	
Submission of abstract for ACTG review	Preferably at least 5 days and no fewer than 72 hours prior to conference organizer deadline[1]	• Send analyses on which abstract is based to ACTG Network PI/chair and vice chair, SC chair and vice chair. • Submit final abstract to ACTG Publications Office, via Submission Central on the ACTG member website, after final team review. • Send final draft to SC chair/vice chair/designated committee reviewer for approval/disapproval and to additional review parties[2] for comments (see *Appendix 3* for ACTG Publications Office abstract review distribution list).	Statisticians Writing Chair ACTG Publications Office
ACTG review of abstract	72 hours prior to deadline	• Review abstract and complete abstract endorsement sheet sent by ACTG Publications Office (see *Appendix 4* for Committee Reviewer Responsibilities). • Submit signed abstract endorsement sheet, which may include additional comments, to ACTG Publications Office upon completion of review.	SC Chair/Vice Chair/designated committee reviewer
Completion of ACTG review	At least 24 hours prior to conference submission deadline	• Communicate SC endorsement and all comments to corresponding and lead author • Respond to review comments (if approved, proceed with next step)— ○ If not approved by the SC chair/vice chair/designated committee reviewer, either revise and resubmit for a second ACTG review a minimum of 24 hours prior to the conference submission deadline, withdraw the abstract from the conference (if already submitted), or send an appeal to the SASC/Executive Committee chairs.	ACTG Publications Office Writing Chair
Submission to conference organizer	Within 5 days after ACTG approval	Submit abstract to the ACTG Publications Office at the time of conference submission	Writing Chair

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Notification of abstract disposition	Within 10 days after notification by conference organizer	Provide a copy of the disposition to ACTG Publications Office. *Failure to notify the ACTG Publications Office that an abstract has been accepted may result in actions by the SC leadership.*	Writing Chair
If abstract is accepted and dissemination of summaries is required by the TSG/SC	At least 48 hours prior to release to the general public	See Section 4.3 table for Executive Summaries and/or Section 4.4 table for CTU/CRS Scientific Summaries	ACTG Network Coordinating Center
If abstract is accepted and development of press releases is found to be required	Prior to conference	See Section 4.5 table for Press Releases	Pharmaceutical, biomedical industry representatives, protocol team, or NIAID/DAIDS
If abstract is not accepted: Revision and resubmission of abstract	Preferably at least 5 days and no fewer than 72 hours prior to the conference organizer deadline	Notify the ACTG Publications Office of abstract rejection prior to resubmission to another conference. If major revisions occur, re-review is required, otherwise the endorsement stands. Submit revised abstracts to the ACTG Publications Office, via Submission Central on the ACTG member website, for a second ACTG review prior to submission to another conference. Team review is required prior to resubmission for ACTG review.	Writing Chair
Preparation of conference presentation	Prior to conference	• Acknowledge the ACTG and include the ACTG logo on presentation materials. The ACTG logo can be found on the ACTG member website, under Shared Resources, General ACTG information, About ACTG folder (https://member.actgnetwork.org/cms/folder/6169). • Circulate final/near-final poster and/or slides to protocol team, including pharmaceutical, biomedical industry, or other external collaborators, for review. Posters and/or slides do not need to be submitted to the ACTG Publications Office for ACTG review.	Writing Team Writing Chair
Dissemination of accepted abstracts	At least 1 day prior to conference start date	Send copies of accepted abstracts to all CTU PIs and CRS Leaders	ACTG Publications Office
Presentation of conference paper	Within 2 weeks following the conference	Send an electronic copy of the finalized presentation to ACTG Publications Office to be posted on the ACTG website.	Writing Chair

[1] *If data not available in timeframe, alternative review process may be determined by SC, SASC, and Executive Committee chairs.*
[2] *Timelines codified in CTA may supersede timelines set in this SOP.*

[3]If the company changes its name, merges with or is acquired by another company, a representative of the new company must receive the manuscript. Timelines and requirements for manuscript review may be superseded by Clinical Trials Agreement stipulations.
[4]SDAC statistician responsible for distributing for SDAC review; SDAC responsibility to ensure distribution of analysis reports to ACTG Network PI/Chair and Vice Chair and SC Chair and Vice Chair for both abstracts and manuscripts.) DAIDS protocol member (Medical Officer) responsible for distributing for internal DAIDS review.

4.3 ACTG Executive Summaries

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Decision to prepare Executive Summary	Near finalization of primary analysis plan, or a preliminary analysis prior to preparation of full primary analysis report, upon conference acceptance or upon journal acceptance	Make decision to prepare an Executive Summary	SC leadership, in consultation with DAIDS, protocol Chair, and/or statistician, and SASC
Preparation of Executive Summary and Participant Summary	Within 60 days after the decision to prepare Executive Summary	• Oversee and contribute to the team's drafting of Executive Summary, based on primary analysis report, or a preliminary analysis prior to preparation of full primary analysis report, and Participant Summary. Draft must state that the material is confidential and not for public distribution. • Urgent summary: submit written request to SC chair, and/or SASC and Executive Committee chairs specifying reason for an altered timeline.	Protocol Chair and team statistician, or designated team member Protocol Team

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Protocol team review	Within 30 days after protocol chair receives final primary analysis (for decisions made during preparation of analysis report) or < 14 days before conference presentation/journal publication	• Send Executive Summary and Participant Summary drafts to CTS for distribution to protocol team, and pharmaceutical, biomedical industry, or other external collaborators if not on team log on for 5-day review. Team members may not disseminate results prior to Executive Summary release. • Receive comments from reviewers. Allowed 2-5 days to incorporate team comments into final drafts. (Timeframe contingent on conference presentation date or anticipated journal publication date.)	Protocol Chair and team statistician, or designated team member
Scientific Committee, ACTG Network PI/Chair, SASC, collaborator, and DAIDS review	Following protocol team review and incorporation of team comments	• Forward final drafts to the DAIDS, the relevant SC leadership, the ACTG Network PI/Chair, and the SASC chair for 5-day review. Summaries cannot be disseminated until approval from all parties is received. • In the event of disagreement, work with the review groups to reach agreement. If agreement cannot be reached, appeals should follow the ACTG appeal and grievance procedure (SOP ACTG -120)	ACTG Network Coordinating Center SC Chair
Dissemination of Final Executive Summary, Participant Summary, and accompanying documents	Upon approval by SC, ACTG Network PI/chair, SASC chair, collaborators, and DAIDS and at least 48 hours prior to public release	Electronically distribute Executive Summary, Participant Summary, and accompanying documents (i.e., press release, question and answer documents and note to physicians) with statement indicating information is embargoed until public presentation or publication (see *Appendix 3* for Executive Summary dissemination list).	ACTG Network Coordinating Center

4.4 ACTG CTU/CRS Summaries

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Preparation and review of CTU/CRS Scientific Summary and Participant Summary	If the decision is made that an Executive Summary is not needed and the summaries are required per the SC leadership.	• Prepare Scientific Summary and Participant Summary. • Review and approve the Scientific and Participant Summaries prior to dissemination.	Protocol Team Relevant SC leadership, ACTG Network PI/Chair, SASC chair, DAIDS, pharmaceutical, biomedical industry, or other external collaborators
Dissemination of CTU/CRS Scientific and Participant Summaries	At least 48 hours prior to the first public presentation of the results	Distribute Scientific Summary with Participant Summary to the CTU PI, CRS Leader, and CTU and CRS Coordinators with a statement indicating that the information is embargoed until public presentation or publication.	CTS

4.5 ACTG Press Releases

4.5.1 If prepared for published or presented abstracts reporting preliminary study results prior to completion of final study results, only data from published/presented abstract is normally permitted for use in press release. Additional data may be included with the express permission of the protocol team and the ACTG Network PI/Chair.

4.5.2 Press releases to be issued by the ACTG on behalf of its own studies should be prepared by the protocol team.

4.5.3 The Protocol team, pharmaceutical, biomedical industry, or external collaborators, and NIAID/DAIDS must work directly with the ACTG Communications Manager, actg.communications@fstrf.org, on all press releases.

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY/PARTIES
Preparation of a press release by pharmaceutical, biomedical industry, or external collaborators*	When study is complete and an abstract is published/presented, but final results and/or primary manuscript are not published or if primary/secondary manuscript is scheduled for publication.	Protocol team members who are aware of press releases in development by pharmaceutical, biomedical industry, or external collaborators should notify the ACTG Communications Manager.	Protocol Team
Request permission to publish a press release	When study is complete and an abstract is published/presented, but final results and/or primary manuscript are not published or if primary/secondary manuscript is scheduled for publication.	Submit the press release, with a request to publish it, to ACTG Publications Office for approval by Protocol Team, SC chair, ACTG Network PI/Chair, the ACTG Communications Manager and NIAID/DAIDS.	Pharmaceutical, biomedical industry, or external collaborators, Protocol Team, or NIAID/DAIDS
Publication of press release	Following approval by protocol team, SC chair, ACTG Network PI/Chair and NIAID/DAIDS	Submit a copy of the published press release to the ACTG Publications Office.	Pharmaceutical, biomedical industry, or external collaborators, Protocol Team, or NIAID/DAIDS

Questions and comments regarding press releases may be directed to the ACTG Communications Manager, actg.communications@fstrf.org

5.0 REFERENCES

5.1 SOP ACTG-109, NWCS Development and Review

5.2 SOP ACTG-106, DACS Development and Review

5.3 SOP ACTG-126, Site Performance Measures and Standards of the Performance Evaluation Committee

5.4 SOP ACTG-107, ACTG Network-Specific Financial Disclosure and Conflict of Interest Procedures

5.5 SOP ACTG-101, Study Closure, Data Cleanup and Study Analysis Preparation

5.6 SOP ACTG-158, Requests for Data from ACTG Studies

5.7 SOP ACTG-120, Appeal and Grievance

5.8 NIH Public Access Policy at http://publicaccess.nih.gov/policy.htm.

5.9 ACTG CTU and CRS Grant numbers at https://member.actgnetwork.org/cms/folder/6211

6.0 INQUIRIES

Questions and comments regarding these procedures may be directed to the ACTG Publications Office at ACTGPublications@partners.org.

7.0 APPENDICES

Appendix 1— Writing Team Guidelines

Appendix 2— Requesting a Manuscript Writing Extension

Appendix 3— Distribution Lists

Appendix 4—Committee Reviewer Responsibilities

Appendix 5— Sanctions

Appendix 6— ACTG Publication Costs

Appendix 1: Writing Team Guidelines

Writing Team Membership

The Protocol Core Team is responsible for forming the writing team, which usually comprises the following parties—

1. Protocol Chair or Co-Chairs
2. Protocol Vice Chair(s)
3. Statisticians
4. Protocol Team investigators
5. Immunologist, virologist, and/or pharmacologist, as appropriate

Guidelines for Masthead Authorship and the Author Order

The masthead should include those who have made significant contributions to the design, conduct, or analysis of the study. Masthead authorship should not be based solely on participation as a protocol team member, data manager, CTS, laboratory staff, field representative, pharmaceutical or biomedical industry collaborators, or other external collaborators, or on the number of study participants accrued to the study. The inclusion of authors, and their roles and authorship order should be determined as the manuscript is in preparation, and finalized by the time the manuscript is ready for submission. In the event of disagreements regarding masthead authorship, the SC leadership should be consulted. If agreement cannot be reached, an appeal should be submitted to the SASC. Any subsequent appeals should follow the ACTG appeals procedure (SOP ACTG-120).

For studies that enrolled subjects from fewer than six institutions one investigator from each institution contributing study participants may be considered for masthead authorship, if journal limitations on numbers of authors will allow.

For studies involving more than six institutions, institutions with high subject enrollment may have one investigator considered for masthead authorship. The address of each co-author should reflect his/her own site. If the protocol chair or vice chair is from a high enrolling institution and is already an author, he/she can place another investigator from that institution on the masthead. In cases where the large numbers of enrollees render the inclusion of a single representative from each site with high accrual infeasible, the team may consider developing an alternative plan for allowing masthead authorship by investigators from participating sites. This plan should be presented to the SASC for consideration prior to the circulation of a draft manuscript for ACTG review.

Journal Criteria for Authors. The number of authors on the masthead of an article may be limited by journal guidelines. Masthead authorship must meet the criteria for the journal.

Masthead Author Relocation. In instances where study work is completed or substantially conducted at one institution and the author relocates to another institution prior to the manuscript being submitted to a journal, both the author's current and former institutions should be cited. It is the responsibility of the relocated author and the site leader of the former CRS to ensure that both institutions are cited in the publication.

Acknowledgment of ACTG, NIAID, and other Support for Annual Reporting and Scientific Contribution Credit

Appropriate acknowledgment of ACTG support is required for annual reporting to sponsor institutes and for ACTG-related manuscripts to receive relevant scientific contribution credit in the annual site and laboratory performance evaluations, in accordance with SOP ACTG 126, respectively.

1. In compliance with the NIH Grants Policy Statement**,** include the following citation in all papers published under the auspices of the ACTG:

   "Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1 AI068634, UM1 AI068636 and UM1 AI106701. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health". Support of collaborating Institutes or Centers (ICs), should be included with this statement, notably the National Institute of Dental and Craniofacial Research (NIDCR) and the National Cancer Institute for OHARA and malignancy studies; National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH) and National Heart, Lung and Blood Institute (NHLBI) for the studies they have supported.

2. In addition to #1, acknowledgement of the participating sites is required as follows:
   - Study-related primary and major secondary manuscripts must include an acknowledgements appendix. Please contact the ACTG Publications Office to obtain names and grant numbers from each participating site. The list of CTU and CRS Grant numbers is available on the ACTG member website under the Publications Resources page, https://member.actgnetwork.org/cms/folder/6211.
     - For studies with CRSs/CTUs that have received support from additional center grants include the following citation:

       "Supported in part by a grant(s) funded by the National Center for Advancing Translational Sciences (or subsequently designated NIH center)"
   - For NWCS and DACS and minor secondary manuscripts, a statement acknowledging the participating clinical research sites of the parent studies is sufficient.

3. Cite the ACTG's sponsor institute and all other NIH institutes that contributed funds to the ACTG's efforts.

Documentation of National Clinical Trial (NCT) Number

ACTG clinical trials are registered with the ClinicalTrials.gov web-based protocol registration system. A unique identifier (NCT number) is provided that should be documented in the final manuscript, according to the journal. The ACTG Publications Office or CTS can be contacted for this number.

Appendix 2: Requesting a Manuscript Writing Extension

If the writing team chair is not able to submit a final manuscript draft to the ACTG Publications Office within 90 days of the protocol chair receiving the final primary or secondary analysis, an additional 30-day extension may be granted by the SC Chair.

The Writing Team Chair must submit a written request for an extension to the ACTG Publications Office at least 2 weeks prior to the deadline and include an explanation for the delay. The ACTG Publications Office will forward the request to the SC chair and SC Coordinator. The SC Coordinator will subsequently provide written notification of the SC's approval or disapproval of the writing extension to the Writing Team Chair and copy the ACTG Publications Office.

If the draft manuscript is not received within 90 days of receipt of the analysis, the SC leadership may impose sanctions (See Appendix 5: Sanctions). The SC Leadership must communicate any sanctions to the ACTG Publications Office.

Appendix 3: Distribution Lists

Manuscript 14-day team review and sign-off distribution list (prior to ACTG review submission)—

For Primary/Secondary Manuscripts:

- Writing Team
- Masthead authors
- Protocol team, to include all current members including SDAC**, DAIDS***, the protocol chairs, and the pharmaceutical and biomedical industry representatives* (if applicable)
    - For substudies, the main study team & substudy team must be included

For NWCS and DACS Manuscripts:

- Masthead authors to include SDAC if SDAC** is a co-author
- Protocol Chair(s) of the parent protocol(s)
- Pharmaceutical and biomedical industry representatives of the parent protocol(s)

*If the company changes its name, merges with or is acquired by another company, a representative of the new company must receive the manuscript. Timelines and requirements for manuscript review may be superseded by Clinical Trials Agreement stipulations.

**SDAC responsibility of statistician to distribute for SDAC review; SDAC responsibility to ensure distribution of analysis reports to ACTG Network PI/Chair and Vice Chair and SC Chair and Vice Chair for both abstracts and manuscripts.)

***DAIDS responsibility of protocol member to distribute for internal DAIDS review.

The ACTG Publications Office can assist with providing the contact information for the appropriate review parties.

ACTG Publications Office manuscript review distribution list—

- SC Chair/Vice Chair/designated committee reviewer*
- ACTG Network PI/Chair
- SASC Chair
- ACTG Network Laboratory PI
- SDAC
- DAIDS
- CTU PIs or CRS Leaders of participating (for primary manuscripts only)

* If a secondary manuscript falls under a different committee than the primary manuscript, a SC chair/vice chair/designated committee reviewer from both committees must review the manuscript.

ACTG Publications Office abstract review distribution list—

- SC chair/Vice Chair/designated committee reviewer
- ACTG Network PI/Chair
- SASC Chair
- ACTG Network Laboratory PI
- DAIDS
- SDAC
- Pharmaceutical Representatives
    - For NWCS and DACS abstracts, pharmaceutical representative(s) of the contributing protocol(s)
- Protocol Chair(s) (if not on the masthead)
    - For NWCS and DACS abstracts , protocol chair(s) of contributing protocol(s)

ACTG Network Coordinating Center Executive Summary Dissemination list—

- CTU PIs and CRS leaders at participating sites (may share summary with IRB if requested)
- Protocol Team
- Director, Therapeutics Research Program, DAIDS
- DAIDS Medical Officer (clinical representative or clinical monitor)
- DAIDS Medical Officer who is a member of the SC responsible for the summary
- ACTG Network PI/Chair
- SASC Chair
- SC Chair
- ACTG Network Coordinating Center SC Leader
- SDAC Section (Scientific Committee) Head
- Industry sponsor (if sponsorship/support is listed on protocol document but no representative on the protocol team distribution list)
- Director, ACTG Network Coordinating Center
- ACTG Network Coordinating Center Clinical Manager
- ACTG Publications Office
- Regulatory Support Center for forwarding to the Food and Drug Administration
- Any site unable to retrieve the electronic information should contact the ACTG Network Coordinating Center to receive a hard copy.

Appendix 4: Committee Reviewer Responsibilities

The decision to approve or disapprove submission of a manuscript to a journal, or an abstract to a conference, is solely that of the SC chair/vice chair, or the designated committee reviewer if the chair and vice chair are conflicted.

The SC Chair/Vice Chair/designated committee reviewer is responsible for the following—

1. Ensuring the scientific integrity of the abstract or manuscript.
2. Ensuring that the writing team adheres to the ACTG publication policies on authorship; ACTG acknowledgment; citation of the protocol number(s); and citation of the NCT number.
3. Ensuring the authors have circulated the manuscript or abstract to the pharmaceutical, and biomedical industry representatives involved with the study during team review; the right to review manuscripts is an important part of the CTA between the pharmaceutical and biomedical companies and the NIAID/DAIDS, acting on behalf of the ACTG.
4. Ensuring that potential conflicts of interest are appropriately acknowledged.
5. Requiring SDAC review, if necessary
6. Confirming that primary and major secondary manuscripts are (a) credited to the ACTG Network LOC, LC, and SDAC grants (b) primarily funded by the Network and (c) contain an acknowledgement appendix containing names and grant numbers for each site. In the event that publication costs (see *Appendix 6* for details) are accrued, these criteria must be met in order for the ACTG Central Group to cover publication costs.
7. Confirming that NWCS and DACS and minor secondary manuscripts are (a) credited to the LOC, LC, and SDAC Network grants and (b) contain a statement acknowledging the participating clinical research sites.
8. Agreeing on substantial changes made to the abstract or manuscript following ACTG review.

Appendix 5: Sanctions

Manuscripts

Potential actions and/or sanctions include but are not limited to appointment of a new Writing Team Chair, deduction of scientific credit points from the relevant CRS or Specialty Laboratory during annual site and laboratory evaluations, respectively; prohibition of the writing team chair from chairing future studies and/or removal of the chair from the protocol or scientific team. In the event that another writing team chair is appointed, but is unable to complete the manuscript publication process, the responsible SC Chair will have the option to appoint a third writing team chair, or to ask the protocol statistician to prepare an Executive Summary of the study results that may be submitted to a relevant journal as a concise communication, brief report, or letter, as appropriate. This decision will be made in conjunction with the SASC and in accordance with the Executive Summary Procedures of this SOP. If a new writing team chair is appointed, the SC Coordinator is responsible for communicating the SC's new manuscript timeline to the new writing team chair and the ACTG Publications Office.

In the event that an author prefers to submit to a journal that consistently does not comply with the NIH timeline for submitting articles to PMC, the SC Chair and/or Network Leadership have the option to restrict the writing team from submitting the manuscript to the referenced journal.

Appendix 6: ACTG Publication Costs

The ACTG Central Group will cover the following publication costs for primary and secondary manuscripts if the SC Chair confirms that they have been (a) primarily funded by the Network, (b) credited to the ACTG Network LOC, LC and SDAC grants, and (c) deposited and signed off by the lead author in the PMC system. *

- Review fees
- Page charges

Any additional author fees charged for approved manuscripts, including costs for publishing in an Open Access journal and charges for color figures, will be reviewed by the Executive Committee and SASC Chairs on a case-by-case basis.

The ACTG will not cover Open Access costs for publishing in journals that do not require Open Access. If submitting a request for the ACTG to cover Open Access costs in a journal that requires Open Access, justification for submitting to an Open Access journal must be provided. If the publication cost is for a color figure(s), provide justification for publishing in color.

The ACTG Central Group will not cover publication costs for NWCS/DACS manuscripts.

Once confirmation is received indicating that the ACTG Central Group will cover the publication costs, the ACTG Publications Office will provide the author with information for the invoice.

Costs associated with ordering reprints will not be covered by the ACTG and remain the responsibility of the author.

*For Method A journals, a signed copy of the copyright transfer agreement as evidence that the publication was NIH supported and confirmation from the publisher on submission date will suffice.

FIRST AMENDMENT
TO THE CLINICAL TRIAL AGREEMENT FOR PROTOCOL ACTIV-2/A5401
BETWEEN
DIVISION OF AIDS (DAIDS),
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)
AND
ELI LILLY AND COMPANY

Subject to full execution, this First Amendment (the "Amendment") is made effective as of the date of last signature (the "Effective Date"), by and between Eli Lilly and Company, having its principal address at Lilly Corporate Center, Indianapolis, Indiana 46285 (the "Company"), and the National Institute of Allergy and Infectious Diseases ("NIAID"), National Institutes of Health ("NIH"), which is part of the United States Government Department of Health and Human Services ("HHS"), as represented by the Division of AIDS ("DAIDS"), having its principal address at 5601 Fishers Lane, Bethesda, Maryland 20852 ("NIAID (DAIDS)") (each a "Party" and together, the "Parties").

WHEREAS, the Parties entered into and executed a Clinical Trial Agreement for the Protocol referenced above, effective July 20, 2020 (the "Agreement"); and

WHEREAS, the Parties desire to amend the Agreement to revise the contacts for the receipt of information regarding the safety and/or toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial.

WHEREAS, the Parties have the authority to amend the Agreement pursuant to its terms.

NOW, THEREFORE, in consideration of the premises, the mutual covenants contained herein and other valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereby agree as follows:

1. Capitalized terms used and not otherwise defined herein will have the meanings ascribed to them in the Agreement to the extent defined therein.

2. Section 3.3.3 of the Agreement shall be deleted in its entirety and replaced with the following:

> 3.3.3 As the manufacturer, Company will, in a timely manner consistent with FDA requirements and during the term of this Clinical Trial, provide NIAID (DAIDS) with any information it now has or may obtain until the receipt of the final Clinical Study Report for the Company Study Product by the Company regarding the safety and/or the toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial. NIAID (DAIDS) will promptly transmit that information to all Investigators. Such information shall be sent to:

(b)(6)
(b)(6)
Government and Public Health Services
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

(b)(6)
PVG Manager
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

Open label/blinded safety reports:

- PVGNIAIDACTIV2@ppdi.com

Unblinded safety reports:

- PVGNIAIDACTIV2@ppdi.com

3. Section 7 of the Agreement shall be deleted in its entirety and replaced with the following:

7. INVESTIGATOR'S BROCHURE (IB)

Company will provide a current IB in eCTD format for all applicable components of the Study Product, and any later revisions and addenda to the IB for the Study Product, including a summary of changes (SOC), to NIAID (DAIDS), as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Section 13 (Confidential Information) of this Agreement. Company agrees to provide NIAID (DAIDS) any updated version of the IB, with the SOC, within fifteen (15) days of issuance. Company will send the IB and SOC to:

(b)(6)
(b)(6)
Government and Public Health Services
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

(b)(6)
Project Management
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

Marianna Manning

PVG Manager
PPD
E-mail: (b)(6)@ppdi.com
Phone: (b)(6)

NIAID (DAIDS), through PPD, will distribute the IB to the Clinical Research Sites. NIAID (DAIDS) will address requests for IBs, including updated versions and SOCs, to:

(b)(6)
(b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Phone: (b)(6)
E-mail: (b)(6)@lilly.com

4. Section 11 of the Agreement, entitled "Data Collection, Analysis and Management," is amended to add a new Section 11.8 to read as follows:

11.8 NIAID (DAIDS) will share data from the Phase II interim analysis (50% of participants through to Day 14), restricting to participants who have completed Day 28, without treatment assignments. The data may be used only to prepare data formatting ahead of receipt of data from the Day 28 graduation analysis.

5. Section 26 of the Agreement, entitled "Notices," is amended to revise Company's regulatory contact as follows:

For regulatory matters:
(b)(6)
Advisor-Regulatory
(b)(6)@lilly.com
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Safety Reports: Mailindata_gsmtindy@lilly.com

Annual Reports: GPSPeriodicReports@Lilly.com

6. Section 28 shall be added to the Agreement and shall read as follows:

28. LICENSURE OF STUDY PRODUCT

The benefit and risk of investigational drugs such as LY3819253 in the COVID-19 population must be assessed in clinical trials. It is Company's intention to

register and launch LY3819253 in countries where Company has conducted clinical trials. If LY3819253 demonstrates a positive benefit risk in the clinical setting, Company will make final determinations regarding if and where to register and launch LY3819253 based on the availability of alternative treatment(s) or vaccine(s) and/or the ability of Company to scale manufacturing and supply product globally.

7. Except as expressly amended by this Amendment, the Agreement shall be unchanged and shall remain in full force and effect in accordance with its terms.

8. This Amendment may be executed in one or more counterparts, each of which will be deemed an original, and all of which together will constitute one and the same instrument.

SIGNATURES BEGIN ON THE NEXT PAGE

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their duly authorized representatives to be effective as of the Effective Date.

Peter S. Kim -S Digitally signed by Peter S. Kim -S
Date: 2020.11.16 13:07:21 -05'00'

(Signature) (Date)

Peter S. Kim, M.D.
Director
Therapeutics Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health

(b)(6)

(b)(6)
cn=(b)(6)
o=Eli Lilly and Company, ou=Trial Capabilities,
email=(b)(6)@lilly.com, c=US
2020.12.02 15:16:45 -05'00'

(Signature) (Date)

(b)(6)
(b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

(Signature) (Date)

(b)(6)
(b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their duly authorized representatives to be effective as of the Effective Date.

Peter S. Kim -S Digitally signed by Peter S. Kim -S Date: 2020.11.16 13:07:21 -05'00'

(Signature) (Date)

Peter S. Kim, M.D.
Director
Therapeutics Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health

(Signature) (Date)

(b)(6)
(b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

(b)(6)
(Signature) 01 DEC 2020
(Date)

(b)(6)
(b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

IND SPONSOR: NIAID (DCR)

CLINICAL TRIAL AGREEMENT

BETWEEN

DIVISION OF CLINICAL RESEARCH (DCR), NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

&

ELI LILLY AND COMPANY

Based on

Protocol ACTIV3/INSIGHT014

A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of
the Safety and Efficacy of Investigational Therapeutics for
Hospitalized Patients with COVID-19
Short Title: Therapeutics for Inpatients with COVID-19 (TICO)

The **National Institute of Allergy and Infectious Diseases ("NIAID")**, an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the **Division of Clinical Research ("DCR")** and **Eli Lilly and Company** (the "Company"), located at Lilly Corporate Center, Indianapolis, IN 46285 (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial designated as Protocol **ACTIV3/INSIGHT014**, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)."

This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). NIAID (DCR) will conduct this Clinical Trial with a consortium of clinical trial networks under the leadership and coordination of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). Other participating networks include the AIDS Clinical Trials Group (ACTG) under the terms of their Award with NIAID, as well as the Prevention and Early Treatment of Acute Lung Injury (PETAL) and the Cardiothoracic Surgery Trial Network (CTSN) under the terms of their Awards from National Heart Lung Blood Institute (NHLBI), and the U.S. Department of Veterans Affairs (VA). In the event that any other Clinical Research Sites funded by NIAID are included in this Clinical Trial in order to complete enrollment, these sites will meet NIAID standards for clinical research sites conducting research sponsored by NIAID. The Clinical Research Sites and their respective Investigators are not parties to this Agreement.

This Agreement sets forth the terms and conditions under which this Clinical Trial will be conducted and managed.

Company and NIAID (DCR) agree as follows:

1. DEFINITIONS

The terms listed in this Section will carry the meanings indicated throughout this Agreement. To the extent that a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code ("U.S.C.") or the Code of Federal Regulations ("C.F.R."), the definition in the U.S.C. or C.F.R. will control.

"**ACTG**" means the AIDS Clinical Trials Group network sponsored and funded by NIAID in accordance with the terms of an Award.

"**Adverse Event**" or "**AE**" means the definition as stated in the Protocol.

"**Affiliate**" means, with respect to Company, (i) any legal entity of which the securities or other ownership interests representing fifty percent (50%) or more of the equity or fifty percent (50%) or more of the ordinary voting power or fifty percent (50%) or more of the general partnership interest are, at the time such determination is being made, owned, controlled, or held, directly or indirectly, by such legal entity; or (ii) any legal entity

which, at the time such determination is being made, is controlling or under common control with, such legal entity. As used herein, the term "control," whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract, or otherwise.

"**Agreement**" means this Clinical Trial Agreement ("**CTA**"), all executed amendments and supplements to this Agreement, and all schedules, appendices and/or addenda to this Agreement.

"Award" means any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between a Government agency and the awardee, who may subcontract with the Clinical Research Sites.

"**CTSN**" means the Cardiothoracic Surgery Trials Network (CTSN) funded by NHLBI in accordance with the terms of an Award.

"**Case Report Form**" or "**CRF**" means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Clinical Research Sites**" means the clinical research sites designated as INSIGHT sites and any other sites described in the introductory paragraph where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Trial**" means a biomedical or behavioral research study of Human Subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, or devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. In this Agreement, Clinical Trial means the clinical trial for the Protocol.

"**Confidential Information**" means confidential scientific, proprietary, business and/or financial information, provided that Confidential Information does not include:

(a) Information that is in the public domain or subsequently enters the public domain through no fault of the receiving Party;

(b) Information that is presently known or becomes known to the receiving Party from its own independent sources, without restriction as to confidentiality or use, from a person having the legal right to disclose the data;

(c) Information that can be established by competent proof was already known and lawfully in the possession of the receiving Party at the time of the disclosure, without restriction as to confidentiality or use;

(d) Information that is independently created or compiled by the receiving Party without reference to or use of the Confidential Information and such independent development can be documented by receiving Party with written records;

(e) Information that is reasonably required by scientific standards for publication of the results of the Clinical Trial (including Clinical Trial methods and/or data) or

any information that is necessary for other researchers to verify the results of the Clinical Trial;

(f) Information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Study Product; or

(g) Information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, or required to be disclosed by a court of competent jurisdiction or governmental authority, provided that the Party required to disclose provides the other Party with prompt written notice and an opportunity (if legally permissible) to obtain a protective order.

"**Critical Event**" means any unanticipated study-related incident that is likely to cause or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity.

"**Data and Safety Monitoring Board**" or "**DSMB**" means an independent group of experts that advises NIAID (DCR) and the Investigators. The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (2) make recommendations to NIAID (DCR) concerning the continuation, modification, or termination of the Clinical Trial.

"**Effective Date**" means the date of the last signature of the Parties executing this Agreement.

"**Electronic Common Technical Document**" or "**eCTD**" means the standard format for electronic regulatory submissions as per 21 U.S.C. § 379k-1, "Electronic Format for Submissions," and as further described in FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," 80 Federal Register 26057 (2015).

"**FDA**" means the U.S. Food and Drug Administration.

"**Government**" means the Federal Government of the United States of America.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. § 46.102(e)(1), a living individual about whom an Investigator conducting research:

(a) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimen; or

(b) Obtains, uses, studies, analyzes or generates Identifiable Private Information or identifiable biospecimens.

"**ICH**" means the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Cited are:
ICH E3: "Structure and Content of Clinical Study Reports."

ICH E6: "Good Clinical Practice: Consolidated Guidance," published in the Federal Register [83 Federal Register 8882 (2018)]. Also referred to as "FDA Good Clinical Practice Guidelines."

"**Identifiable Private Information**" or "**IPI**" about a Human Subject means private information from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**IND**" means an "**Investigational New Drug Application**," filed in accordance with 21 C.F.R. Part 312, under which clinical investigation of an experimental drug or biologic (Study Product) is performed in Human Subjects in the U.S., or intended to support a U.S. licensing action.

"**INSIGHT**" means the International Network for Strategic Initiatives in Global HIV Trials funded under combination of (1) a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI) and (2) an Award from NIAID to the University of Minnesota.

"**Institutional Review Board**" ("**IRB**") or "**Independent Ethics Committee**" ("**IEC**") means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects, and 21 C.F.R. Part 56, Subpart C: IRB Functions and Operations, as amended April 1, 2013, and other applicable regulations, an independent body comprising medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of the Human Subjects involved in a clinical trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**Invention**" means any invention or discovery that is or may be patentable or otherwise protectable under Title 35 of the U.S.C.

"**Investigator**" means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Study Product to a Human Subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, Investigator means the individual(s) identified as responsible for the conduct of the Clinical Trial at any of the participating Clinical Research Sites.

"**Investigator's Brochure**" or "**IB**" means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Study Product, including animal screening, preclinical toxicology and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the Study Product or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Study Product.

"Leidos Biomedical Research" means the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory activities related to NIAID (DCR)'s

clinical research. Leidos operates pursuant to a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI).

"**Office for Human Research Protections**" or "**OHRP**" means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"**Patent**" means any issued U.S. patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

"PETAL" means Prevention and Early Treatment of Acute Lung Injury, a clinical trials network funded by NHLBI in accordance with the terms of an Award.

"**Protected Health Information**" or "**PHI**," as defined in 45 C.F.R. Parts 160 and 164, under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), includes any *individually identifiable* health information. *Identifiable* refers not only to data that is explicitly linked to a particular individual; it also includes health information with data items which reasonably could be expected to allow individual identification.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV3/INSIGHT014, "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO) " and any company/product specific associated appendices. The Protocol describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. The Agreement will be governed by the most recent version of the Protocol, and should the Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement, the terms of the Agreement will govern.

"**Protocol Team**" means the team responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. The Protocol Team will include the protocol chair (an Investigator), representatives from Company, other Investigators, representatives from NIAID (DCR), and the persons involved with statistical and data analysis for the Clinical Trial. Participation on the Protocol Team will be as agreed by the Parties and will take into account any special requirements of the Protocol design.

"**Sponsor**" means, in accordance with the definition in 21 C.F.R. § 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with Study Product. The Office of Clinical Research Policy and Regulatory Operations

within the NIAID Division of Clinical Research is the IND holder and sponsor of record for this agreement. Additionally, in accordance with 21 C.F.R. § 312.52(a), several sponsor responsibilities will be transferred to the University of Minnesota Statistical and Data Management Center and to Leidos Biomedical Research.

"**Statistical and Data Management Center**" or "**SDMC**" means the data management center at the University of Minnesota responsible for providing statistical and data management services for INSIGHT clinical trials, including the Clinical Trial that is the subject of this Agreement in accordance with the terms of a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI)..

"**Study Product**" means, in accordance with 21 C.F.R. § 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301, *et seq*., Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended. In this Agreement, LY3819253 is referred to as the Study Product.

"VA" means the U.S. Department of Veterans Affairs.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 Company acknowledges that NIAID and NHLBI fund the Clinical Research Sites under Awards, and therefore, the Clinical Research Sites have certain existing contractual or other legal obligations to NIAID and NHLBI.

2.2 Company will not provide any funding or material for any aspect of the Clinical Trial to any Clinical Research Site participating in the Clinical Trial without prior written notification to NIAID (DCR). In addition, subject to Section 14.4 of this Agreement, Company will not enter into any separate agreements, including, but not limited to, material transfer agreements, with the Clinical Research Sites or the Investigators at the Clinical Research Sites that interfere with the conduct of this Clinical Trial.

2.3 NIAID (DCR) hereby certifies that it did not and will not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:
- (i) debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or
- (ii) suspended by OHRP as a clinical research site under 45 C.F.R. Part 46.

2.3.2 Any person convicted of a felony under federal law for conduct:
- (i) relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application (NDA), Biologics License Application

(BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or

(ii) otherwise relating to the regulation of any drug product or medical device under the FDCA.

2.3.3 Any person performing services in connection with this Clinical Trial who has been disqualified as a clinical investigator under 21 C.F.R. § 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required by 21 C.F.R. § 312.53.

2.4 If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party immediately.

2.5 The Awards require that the Investigators at Clinical Research Sites conduct the Clinical Trial in accordance with applicable provisions of ICH E6: FDA Good Clinical Practice Guidelines, and requires that they comply with all applicable U.S., foreign government, state and local laws, regulations and guidelines. NIAID (DCR) will require that Investigators and Clinical Research Sites comply with all applicable anti-bribery laws in the countries where Investigator(s) and Clinical Research Site(s) have their principal place of business and where activities are conducted under this Agreement. Additionally, NIAID (DCR) will require that Investigator(s) and Clinical Research Site(s), comply with the U.S. Foreign Corrupt Practices Act, as revised, which generally prohibits the offer, promise, payment or giving of anything of value either directly or indirectly to any government official for the purpose of obtaining or retaining business or any improper advantage. For purposes of this section, "government official" means any official, officer, representative, or employee of, including any doctor employed by, any non-U.S. government department, agency or instrumentality (including any government-owned or controlled commercial enterprise), or any official of a public international organization or political party or candidate for political office. Additionally, if Investigator(s) and Clinical Research Site(s), or any of their owners, directors, employees, agents, and consultants are government officials, NIAID (DCR), on behalf of itself and the Investigators and Clinical Research Sites agrees that Company's supply of the Study Product in connection with this Agreement is not intended to influence any decision that any individual may make in his capacity as a government official. NIAID (DCR) further represents on behalf of Investigator and Clinical Research Site that they, their owners, directors, employees, agents, or consultants will not directly or indirectly offer to pay, promise to pay or give anything of value to any government official for purposes of (i) influencing any act or decision of such government official in his official capacity; (ii) inducing such government official to do or omit to do any act in violation of the lawful duty of such official; (iii) securing any improper advantage; or (iv) inducing such government official to use his influence with the government or instrumentality thereof to affect or influence any act or decision of the government or such instrumentality with respect to any activities undertaken relating to this Agreement. NIAID (DCR) agrees on behalf of itself and Investigators and Clinical Research Sites that Company's provision of

the Study Product in connection with this Agreement is not intended to influence any decision Investigators and Clinical Research Sites, may make regarding the prescription of Company medicines or to otherwise influence any pending or future Company business

2.6 Company agrees that this Protocol will be conducted only at sites as defined by NIAID (DCR) and collaborating networks. However, Company can conduct, at its own expense and under its own IND, additional clinical trials with the Study Product, at non-NIAID funded sites. Company agrees to inform NIAID (DCR) in writing of any other clinical trials it may support for the use of the Study Product that would compete with this Clinical Trial for the same Human Subject population.

2.7 If Protocol-specified assays that are specific to the Company and are expected to be included in a regulatory submission are performed in laboratories not monitored by NIAID (DCR), Company warrants that such laboratories will comply with applicable Good Clinical Laboratory Practice (GCLP) and all applicable regulatory requirements. Company will provide NIAID (DCR) with results of such assays and upon request, provide documentation to support that the testing and laboratory operations are compliant with applicable GCLP and all applicable regulatory requirements. NIAID (DCR), through its contractor, may audit the laboratory(ies) to ensure compliance with applicable GCLP and all applicable regulatory requirements. All biospecimens sent to the Company in accordance with this Section 2.7 will remain in the custody of the Company. Company shall be the custodian of the data produced by the Company using such samples and will have the exclusive right to use such data for purposes of seeking regulatory approval of the Study Product. The Company will share the data produced by the Company under this Section 2.7 with NIAID (DCR) and NIAID (DCR) will have the right to use the data for non-commercial purposes.

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND.** NIAID (DCR) will submit an IND covering the Protocol to the FDA. The IND will satisfy all of the requirements of the FDA, and, as applicable, will comply with eCTD format requirements. Company agrees to provide all requested documents to NIAID (DCR) in eCTD format. Company will provide a letter granting the FDA permission to cross-reference Company's pertinent Master File (MF), New Drug Application (NDA), Biologics License Application (BLA), and/or INDs in support of the NIAID (DCR)'s IND, and in return, NIAID (DCR) will also provide a letter to Company, if requested, granting the FDA permission to cross-reference the IND filed by NIAID (DCR) for this Clinical Trial. NIAID (DCR) will provide a copy of all IND submissions to Company at the time they are submitted to the FDA. Any Confidential Information of another party will be removed.

3.2 **Clinical Research Site Monitoring.** NIAID (DCR) or their designeee, will be responsible for Clinical Research Site monitoring in accordance with the clinical monitoring plan. Monitoring will be done in compliance with applicable provisions of

the FDA regulations. NIAID (DCR) will communicate any Critical Event findings from clinical monitors to Company in a timely manner.

3.3 **Adverse Event Reporting.**

3.3.1 NIAID (DCR) will collect Adverse Event reports according to the procedure outlined in the Protocol and in accordance with 21 C.F.R. § 312.32. The Clinical Research Sites will report Adverse Events to NIAID (DCR) in a timely manner and according to the Protocol and Protocol Instruction Manual. NIAID (DCR) will assume responsibility for the reporting of Adverse Events to the FDA and will provide copies of all of the safety reports to Company.

3.3.2 NIAID (DCR) will report all unexpected Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the FDA and Company on a timely basis consistent with 21 C.F.R. § 312.32 and the Protocol. NIAID (DCR) will report other serious and non-serious adverse events to the FDA and to Company on a timely basis consistent with 21 C.F.R. § 312.33. NIAID (DCR) will report all Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the Company at the Safety Reports Address listed in the Contacts section within fifteen (15) days of awareness. Company agrees not to contact the Clinical Research Sites directly for information related to Adverse Events. Company shall contact the NIAID (DCR) Safety Office for information related to SAEs:

NIAID Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
Email: rchspsafety@mail.nih.gov

3.3.3 As the manufacturer, Company will, in a timely manner consistent with FDA requirements and during the term of this Clinical Trial, provide NIAID (DCR) with any information it now has or may obtain in the future regarding the safety and/or the toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial. NIAID (DCR) will promptly transmit that information to all Investigators. Such information shall be sent to:

NIAID Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
Email: rchspsafety@mail.nih.gov

3.3.4 During the course of the study, if Company is requested by a regulatory agency to unblind an SAE report, the NIAID (DCR) will collaborate with Company to determine whether the report can be unblinded without undermining the scientific integrity of the Clinical Trial. NIAID (DCR) will provide the blinding codes for study subjects randomized to the Study Product or the placebo to the Study Product to Company when all data forms have been keyed into the database for all subjects, data cleaning has been completed, and the Protocol Team has declared the study data set to be complete.

3.4. **Pregnancy Reporting.** NIAID will report pregnancies with respect to Study Product no later than thirty (30) days of becoming aware of such events.

4. SAFETY MONITORING

Data and Safety Monitoring Board (DSMB). A NIAID DSMB will monitor this Clinical Trial as described in the Protocol. NIAID will notify Company in advance of any DSMB review. NIAID will provide recommendations derived from the DSMB to Company.

5. FDA MEETINGS/COMMUNICATIONS

5.1 With respect to any discussions with the FDA involving data obtained from this Clinical Trial under NIAID (DCR)'s IND, NIAID (DCR), in consultation with Company, will take the initiative in arranging meetings or conference calls with the FDA. Formal meetings with the FDA concerning the Clinical Trial design and/or data will be discussed and agreed upon in advance by Company and NIAID (DCR). Company will have the right to participate in all formal meetings with the FDA. Company agrees not to contact the FDA independently of NIAID (DCR) concerning this Clinical Trial. However, Company may contact the FDA on separate product-related issues. NIAID (DCR) will provide Company with copies of all transmittal letters for IND submissions, and formal questions and responses that have been submitted to the FDA. Any Confidential Information of another party will be removed.

5.2 Company will promptly notify NIAID (DCR) of:

(a) Any FDA correspondence related to the Protocol that is received by Company, or its Affiliates; and
(b) FDA enforcement actions directly related to the Protocol or the Study Product directed toward Company or its Affiliates, including, but not limited to, warning letters, seizures, or recalls; injunctions/consent decrees; rejection of regulatory submissions or withdrawal of approval for a product; and
(c) Criminal investigations; and
(d) Proceedings to debar Company or its Affiliates or individuals employed under a contract to Company and/or its Affiliates.

5.3 Company will also promptly notify NIAID (DCR) of any action taken by the FDA regarding manufacturing of the Study Product that would impact the safety of Human Subjects in the Clinical Trial.

6. SUPPLY, DISTRIBUTION AND USE OF STUDY PRODUCT

6.1 **Supply.** NIAID (DCR) shall provide Company with an estimate of the quantity of Study Product that will be required to complete the Protocol. Company will supply the Study Product to NIAID (DCR) without charge and in quantities and conditions sufficient to complete the Protocol and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Study Product. Company will be responsible for labeling the Study Product used in the Clinical Trial.

6.2 **Distribution.**

6.2.1 Company will ship the Study Product to a central distribution site(s) to be arranged by NIAID, or the Clinical Research Sites, as mutually agreed by the Parties. Company and NIAID responsibilities regarding the Study Product are further set forth in Appendix 1 Quality Procedures attached hereto and fully incorporated herein. Company will provide specific storage and/or shipping instructions for the Study Product to NIAID (DCR), the central distribution site(s), and/or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. Company warrants that any packaging for hazardous material, provided by Company, meets Department of Transportation regulatory requirements for use at all Clinical Research Sites. Incoterms to be delivery at place 2020.

6.2.2 The Study Product must be received by the central distribution site(s) or Clinical Research Sites in usable condition and accompanied by Material Safety Data Sheet (MSDS), specific storage and shipping instructions, stability and/or expiration dating information, Certificate of Analysis (CoA) and the Certificate of Compliance (CoC).

6.2.3 If there is evidence that the Study Product that arrived at the central distribution site(s) or Clinical Research Sites has not been maintained according to the defined shipping instructions, or is potentially adulterated, NIAID (DCR) will contact Company to inform it of the condition of the received Study Product and to determine if the Study Product is usable or if it must be replaced. If the Study Product must be replaced, Company will replace it at no cost to NIAID (DCR), the central distribution site(s), or the Clinical Research Sites.

6.3 **Use.** NIAID (DCR) will not transfer the Study Product to parties other than the central distribution site(s) or the Clinical Research Sites, nor will NIAID (DCR) chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed in writing by the Parties. NIAID (DCR), pursuant to the Awards, will ensure that the Investigators: (i) use the Study Product only in accordance with the

Protocol and for no other purpose; (ii) do not transfer the Study Product to any parties except Company, the central distribution site(s), or the Clinical Research Sites; and (iii) do not chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed to, in writing, by the Parties.

6.4 **Study Product Return.** Upon completion of the Protocol, NIAID (DCR), will ensure destruction or, at Company's request, return any unused Study Product to Company.

6.5 **Warranty.** Company represents and warrants that the Study Product supplied meets the specifications cited in the CoA and CoC provided.

6.6 **Source.**

6.6.1 In the event Company elects to terminate its development of Study Product for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to NIAID (DCR) within ninety (90) days of discontinuation then Company will provide NIAID (DCR) with Study Product sufficient to complete the Clinical Trial in the manner described in the Protocol.

6.6.2 The Parties also agree that should this Agreement be terminated prior to completion of the Protocol, the Protocol will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol and Company will supply enough Study Product to complete the Protocol.

7. INVESTIGATOR'S BROCHURE (IB)

Company will provide a current IB in eCTD format for all applicable components of the Study Product, and any later revisions and addenda to the IB for the Study Product, including a summary of changes (SOC), to NIAID (DCR), as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Section 13 (Confidential Information) of this Agreement. Company agrees to provide NIAID (DCR) any updated version of the IB, with the SOC, within fifteen (15) days of issuance. Company will send the IB and SOC to the NIAID (DCR) to the attention of the NIAID contact for regulatory matters identified in Article 26. NIAID (DCR), through the SDMC, will distribute the IB to the Clinical Research Sites. NIAID (DCR) will address requests for IBs, including updated versions and SOCs, to:

(b)(6) (b)(6)
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Phone: (b)(6)
E-mail: (b)(6)@lilly.com

8. PROTOCOL DEVELOPMENT AND REGISTRATION

8.1 The Parties agree that enrollment in the Clinical Trial will not start until the version of the Protocol to be used has been reviewed in advance by Company, accepted by the Protocol Team, approved by the relevant IRB(s)/IEC(s) and NIAID (DCR) in writing, submitted to the FDA, and any clinical hold issues have been responded to satisfactorily.

8.2 The Parties agree that any alteration in or amendment to the Protocol must be accepted by the Protocol Team, approved in writing by the relevant IRB(s)/IEC(s) and NIAID (DCR), and submitted to the FDA prior to such alteration or amendment becoming effective.

8.3 **Protocol Registration.** All NIAID (DCR)-sponsored network protocols which include the informed consent must meet all federal mandates as well as NIAID (DCR) requirements to ensure the welfare of Human Subjects in the Clinical Trial.

Each Clinical Research Site, prior to participating in any NIAID (DCR)-sponsored study, must submit its informed consent to the NIAID (DCR) or designee for review prior to submission to the IRB.

9. CASE REPORT FORM DEVELOPMENT

NIAID (DCR), through the SDMC, will be responsible for the development and subsequent revisions, if any, of the Case Report Forms with appropriate review and comment by the Protocol Team.

10. HUMAN SUBJECTS PROTECTION

10.1 NIAID (DCR) and Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The informed consent of each Human Subject participating in the Clinical Trial at a Clinical Research Site will be obtained prospectively using an informed consent process. The sample informed consent document may be reviewed in advance by Company and shall be approved by NIAID (DCR) and all appropriate IRB(s)/IEC(s).

10.2 NIAID (DCR) and Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46, Protection of Human Subjects. Therefore:

10.2.1 NIAID (DCR) and Company will maintain the confidentiality of IPI, including PHI, collected under the Clinical Trial and protect the privacy of the individual Human Subjects unless disclosure is required by law.

10.2.2 NIAID (DCR) and Company may inspect, but not copy, Human Subjects' medical records that might also include information not directly connected to this Clinical Trial. However, NIAID (DCR) and Company agree that this information

will remain confidential and will not be used for any purpose other than confirmation of Clinical Trial data or to resolve study-related injury issues.

10.2.3 NIAID (DCR) and Company agree that neither Party will use, nor will it allow its contractors to use, IPI for any purpose not stated in the Protocol, without the consent of the other Party and local site IRB/IEC approval unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative. NIAID (DCR) will ensure that the Investigators do not use IPI for any purpose not stated in the Protocol and informed consent document without the written consent of both Parties and appropriate IRB/IEC approval, unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative.

10.2.4 NIAID (DCR) and Company agree to comply with the determinations of all IRB(s)/IEC(s) overseeing this research.

10.2.5 Biospecimens and data related to biospecimens provided to Company during and after the Clinical Trial will be coded.

11. DATA COLLECTION, ANALYSIS AND MANAGEMENT

11.1 The Clinical Research Sites will be responsible for gathering the data and submitting it to the SDMC. The Protocol Team, which includes Company representatives, will be responsible for the scientific reporting of the data.

11.2 NIAID (DCR), through the SDMC, will have responsibility for the data management: collection, entry and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

11.3 It is the responsibility of both Company and the NIAID to protect the scientific integrity of the ACTIV 3 study. Doing so requires maintaining the study blind throughout both stages of the ACTIV 3 protocol. Access to unblinded data at the end of stage 1 will be made available only to the DSMB. Based on predefined guidance in the statistical analysis plan (SAP), the DSMB will make a determination if the study agent can continue to stage 2. If the study agent does not proceed to stage 2, the initial stage 1 data (at the time of interim) for the Study Product and the stage 1 data for the Study Product at the end of the 90 day follow-up period will be made available to Company and the Parties will collaborate to publish the results of the stage 1 portion of the study in a timely manner. The DSMB will make a timely recommendation on the timing of the availability of the study data for the control group if the placebo control group is shared with other agents. The parties will work together in good faith to ensure the timely release of the stage 1 data with input from the DSMB. The study team will remain blinded throughout.

11.4 All data obtained from the Clinical Trial will be in the custody of the Investigator or the

Clinical Research Site, as applicable, which produces such data. However, other than Company, its contractors and its designees, any party wanting to review or use the data obtained from the Clinical Trial for purposes of seeking regulatory approval of the Study Product will obtain the prior written permission of Company.

11.5 Upon completion of the data analyses, the NIAID will authorize the SDMC to transfer to the Company a copy of the complete data analysis set in a machine-readable format to be determined jointly by the Parties. If Company requires that the data be provided in a customized format(s), Company will pay for all costs associated with the customized data format(s).

11.6 Subject to the right of NIAID (DCR) and the Investigators to publish the data from this Clinical Trial as set forth in the Publications and Press Releases Section of this Agreement, Company has the right to utilize the data reports and associated data from this Clinical Trial in its possession for all legitimate business or regulatory purposes. NIAID (DCR) and/or Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA and the Securities and Exchange Commission (SEC), for all legitimate public health, regulatory or business purposes. Except for information related to regulatory or safety issues or under emergency circumstances where it is not practicable to do so and to the extent permitted by law, NIAID (DCR) will not release information regarding the Clinical Trial to governmental organizations without prior notification to Company.

11.7 NIAID (DCR), through its contractor, will be responsible for preparing the final Clinical Study Report in accordance with ICH E3, "Structure and Content of Clinical Study Reports" and will provide a copy of the Clinical Study Report for the Company Study Product to Company. NIAID (DCR) will provide such Clinical Study Report in draft form for Company's review prior to its finalization. The provision of such Clinical Study Report to Company by NIAID (DCR) is not conditioned upon the graduation of the Study Product.

12. PUBLICATIONS AND PRESS RELEASES

12.1 Any publications based on the results of the Clinical Trial and originating from NIAID (DCR) or the Investigators will conform to the latest version of the INSIGHT Publications Standard Operating Procedure. Unless requested otherwise by Company, NIAID (DCR) will acknowledge Company as the source of the Study Product in any NIAID (DCR) publication resulting from the Clinical Trial and will ensure that the Investigators do the same in their publications resulting from the Clinical Trial.

12.2 Recognizing that employees of either Party may play an important role in the design, analysis and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the generally accepted customs pertaining to authorship. NIAID (DCR) will ensure that the Investigators include appropriate individuals from both Parties in their publications resulting from the Clinical Trial.

12.3 Each Party will provide, and NIAID (DCR) will ensure that the Investigators provide, a copy of any abstract or manuscript to the other Party prior to submission for publication with sufficient time for review and comment, as outlined in the INSIGHT Publications Standard Operating Procedure [Manuscripts: ten (10) days; Abstracts: five (5) days]. The publication or other disclosure may be delayed for up to thirty (30) additional business days for manuscripts and up to five (5) business days for abstracts, upon written request by either Party as necessary to preserve U.S. or foreign Patent or other intellectual property rights. At either Party's request during its period of review specified above, said Party's Confidential Information shall be removed from such publication or disclosure. If a Party requests redaction of its Confidential Information, the Party will make reasonable efforts to supply substitute non-confidential information to the publishing Party in order to allow the publication to go forward. Each Party agrees that, following the receiving Party's review of the manuscript and/or abstract for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish, present or use any Clinical Trial data. Notwithstanding the timelines described above, the Parties agree that expedient publication of the Clinical Trial results is necessary for the public good and the Parties agree to work in good faith to allow expeditious publication of the Clinical Trial results.

12.4 Each Party will provide, and NIAID (DCR) will ensure that the Investigators provide, a copy of any proposed press release to the other Party for review at least five (5) business days in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish the press release.

13. CONFIDENTIAL INFORMATION

13.1 Either Party may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct the Clinical Trial. The disclosing Party will place a confidentiality notice on all the Confidential Information. The disclosing Party will reduce confidential non-written communications to writing within thirty (30) business days of first disclosure. Regarding oral disclosures of Confidential Information, if a Party does not reduce oral Confidential Information to writing, the Party must verbally provide notice of the confidential nature of the oral disclosure at the time it is disclosed for the oral Confidential Information to be considered confidential under this Agreement. Each Party receiving Confidential Information agrees that any information so designated will be used by it only for the purposes of the Clinical Trial. Any Party may object to the designation of information as Confidential by the other Party.

13.2 Unless expressly provided otherwise, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other

person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA), 5 U.S.C. § 552, or other applicable laws and/or regulations to disclose the Confidential Information, except that NIAID (DCR) and Company may disclose Confidential Information to those of their representatives, agents, officers, grantees, contractors, consultants, employees, and potential Clinical Research Sites (collectively, "Agents") to the degree necessary to conduct the Clinical Trial. The Parties will ensure that their respective Agents maintain the confidentiality of Confidential Information in accordance with the terms of this Agreement.

13.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. Current NIH policy requires that a brief synopsis, the enrollment status and study results for all NIH-funded clinical trials be posted in the ClinicalTrials.gov registry of clinical studies, available through the NIH website. NIAID (DCR) shall be responsible for submitting information to ClinicalTrials.gov after review of information from the Study Product by Company's representative on the Protocol Team.

13.4 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given an opportunity to seek a court order to enjoin from disclosure.

13.5 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above, or five (5) years after the expiration or termination date of this Agreement. Either Party may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

14. INTELLECTUAL PROPERTY

14.1 Ownership of any invention made solely or jointly by NIAID (DCR), the Clinical Research Sites and Investigators, or other NIAID (DCR) contractors or grantees as a consequence of conducting the Clinical Trial and involving the Study Product, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party claims by virtue of this Agreement any right, title, or interest in or to any issued Patents or pending Patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by Company to NIAID (DCR) with respect to the Study Product, other than the limited right to use the Study Product for the performance of the Protocol in accordance with the terms of this Agreement.

14.2 **NIAID (DCR) Intellectual Property.**

14.2.1 The Government will retain title to any Patent or other intellectual property rights in inventions made by NIAID (DCR) employees in the course of the Clinical Trial.

14.2.2 NIAID (DCR) agrees to notify Company of any such Invention and is willing to disclose it to Company under an appropriate confidentiality agreement. Company may apply for exclusive license rights to any patentable Invention made by NIAID (DCR) employees that might arise during the clinical research and the NIH will consider Company's application for a license consistent with 37 C.F.R. Part 404.

14.3 **Company Intellectual Property.** Company will retain title to any Patent or other intellectual property rights in Inventions made by its employees during the course of the Clinical Trial.

14.4 **Clinical Research Site/Investigator Intellectual Property.** This Agreement does not grant or preclude intellectual property rights, including, but not limited to, Inventions made by INSIGHT, the Investigators, or other Government contractors or grantees during the course of the Clinical Trial. Company may enter into a separate agreement with the Clinical Research Sites or Investigators regarding intellectual property rights that do not interfere with the conduct of this Clinical Trial or contradict the terms of this Agreement.

14.5 **Joint NIAID-Company Intellectual Property.** NIAID and Company will have joint intellectual property rights in Inventions made jointly by their employees during the course of the Clinical Trial.

15. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

16. LIABILITY, INDEMNIFICATION AND INSURANCE

16.1 **Liability.** Activities carried out under this Agreement are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) as implemented under the amended declaration, "Public Readiness and Emergency Preparedness Act Coverage for medical countermeasures against COVID–19," issued on March 17, 2020 (85 Federal Register 15198). The PREP Act provides immunity from liability claims against manufacturers, distributors, program planners and other qualified persons ("Covered

Persons") arising from the administration and use of covered countermeasures, as specified in a declaration by the Secretary of HHS ("Secretary") [See section 319F-3 of the Public Health Service Act (42 U.S.C. §247d-6d)]. The exception to this immunity is acts of willful misconduct by the Covered Persons. The Study Product is considered a drug to treat, prevent or mitigate COVID-19, and as such is a covered countermeasure under the Secretary's declaration. Informed consent forms used in the Clinical Trial will include a sufficient description of the PREP Act for participants to understand that all Covered Persons have immunity from liability under the PREP Act, and what compensation may be available under the PREP Act Countermeasure Injury Compensation Program [See section 319F-4 of the Public Health Service Act (42 U.S.C. §247d-6e)]. To the extent that PREP Act coverage is not available, each Party shall be liable for any loss, claim, damage or liability that it incurs as a result of its direct activities under this Agreement, except that NIAID (DCR), as an agency of the U.S. Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171.

16.2 **Indemnification.** NIAID is prohibited under the Anti-Deficiency Act, 31 U.S.C. § 1341 from indemnifying Company for any losses incurred as a result of this Clinical Trial. Each Party will be liable for the losses, claims, damages or liabilities that it incurs as a result of its activities under this Agreement. Company's right and obligation to defend NIAID and Company's control over the defense and settlement of any claim against NIAID will be subject to the consent of NIAID and the Department of Justice.

To the extent that PREP Act coverage is not available, Company will defend, indemnify and hold harmless the Government's grantees and contractors and their respective agents and employees ["Indemnitee(s)"] from any and all liabilities, damages, losses, claims, action, suits and expenses, including attorneys' fees and court costs (collectively "Claims") to the extent caused by the administration or use of the Study Product during the course of the Clinical Trial, provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if each of the following conditions is met:

16.2.1 The Claim was not proximately caused by the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, any written instructions from Company, and this Agreement.

16.2.2 The Claim was not caused by the gross negligence, recklessness or willful misconduct of any Indemnitee, provided that any action properly taken by the Indemnitee in compliance with the Protocol or written instructions from Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if a Claim is jointly caused by the negligence of any Indemnitee and the administration or use of the Study Product, then Company will provide defense and indemnification to the extent the Claim was caused by the administration of the Study Product.

16.2.3 Company is promptly notified of the Claim, provided that the failure to give such notice will not abrogate or diminish Company's defense and indemnity obligation

if Company has or receives knowledge of the existence of the Claim by any other means or if such failure does not prejudice Company's ability to defend the Claim.

16.2.4 Company will have sole control over the defense and settlement of the Claim(s) directed against Company.

16.2.5 Company will have the right to select defense counsel and to direct the defense and settlement of the Claim(s) directed against Company.

16.2.6 Company will provide a diligent defense against and/or settlement of any Claims for which defense and indemnification are provided under this Agreement whether such Claims are rightfully or wrongfully made. Company will have the right to settle such Claims, at Company's sole expense and in Company's sole discretion. Indemnitee(s) will fully cooperate, at Company's expense, with Company and its legal representatives in the investigation and defense of any Claim for which defense and indemnification are provided under this Agreement.

16.2.7 The Indemnitee(s) will at all times have the right to fully participate in the defense of any Claim at their own expense and for their own account.

16.3 **Insurance.** Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the research related injury and indemnification obligations assumed under this Agreement. Upon request, Company will provide evidence of its insurance or self-insurance to NIAID (DCR).

17. DISPUTE RESOLUTION

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the dispute will be referred to the Director of DCR**,** NIAID (or his/her designee) and an appropriate authorized representative of Company for resolution. If the Director of DCR (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute through good faith negotiations within thirty (30) days, the dispute will be referred to the Director of NIAID (or his/her designee) and the authorized representative of Company. If the Director of NIAID (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute, either Party may pursue any and all administrative or judicial remedies that may be available.

18. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the

other Party, enter into any contract, warranty, or representation as to any matter. Neither Party will be bound by the acts of the other Party.

19. NON-ENDORSEMENT

By entering into this Agreement, NIAID (DCR) does not directly or indirectly endorse any product or service provided, or to be provided, by Company. Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However, Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

20. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

21. SURVIVABILITY

The provisions (Clinical Research Sites and Investigators), (Investigational New Drug Application Sponsorship), (Supply, Distribution and Use of Study Product), (Human Subjects Protection), (Data Collection, Analysis and Management), (Publications and Press Releases), (Confidential Information), (Intellectual Property), (Liability, Indemnification and Insurance), (Dispute Resolution), (Independent Contractors), (Non-Endorsement), (Amendments) and this Section (Survivability) will survive the expiration or earlier termination of this Agreement.

22. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement, including the Appendix attached hereto and incorporated herein, constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement. The provisions of this Agreement are severable and, in the event that any provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

23. ASSIGNMENT

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without prior written notification to the other Party. The terms and conditions of this Agreement shall be binding on and inure to the benefit of the permitted successors and assigns of the Parties.

24. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

25. TERM AND TERMINATION

Unless terminated sooner in accordance with this Term and Termination Section, this Agreement will expire upon completion of the Clinical Trial. The Parties may terminate this Agreement at any time by mutual written consent. Either Party may unilaterally terminate this Agreement at any time by giving written notice at least thirty (30) days prior to the desired termination date. The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol, and Company will supply enough Study Product to complete the Clinical Trial. In the event that Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution, Company must notify NIAID (DCR) within at least thirty (30) days of the dissolution.

26. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt) or via facsimile followed by confirmational hard copies sent via international courier when it is necessary to receive or deliver documents within a very short period of time [less than one (1) day].

For Company:

(b)(6) (b)(6)
(b)(6) @lilly.com
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

For regulatory matters:

(b)(6) (b)(6)
(b)(6) @lilly.com
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Safety Reports: Mailindata_gsmtindy@lilly.com

Annual Reports: GPSPeriodicReports@Lilly.com

For technical matters:

(b)(6) (b)(6)
(b)(6) @lilly.com
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

For NIAID (DCR):

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
5601 Fishers Lane, Suite 6D
Rockville, MD 20892-9804
Phone: (b)(6)
Email (b)(6) @niaid.nih.gov

For regulatory matters:

John Tierney, R.N., M.P.M
Clinical Research Oversight Manager
Office of Clinical Research Policy and Regulatory Operations
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9820
Rockville, MD 20852
Phone: (b)(6)

E-mail: (b)(6) @niaid.nih.gov

For clinical matters:

Elizabeth Higgs, M.D.
Global Health Science Advisor
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9802
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6)

27. COUNTERPARTS

This Agreement may be executed in counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. Signatures to this Agreement transmitted by fax, by electronic mail in portable document (.pdf) format, or by any other electronic means intended to preserve the original graphic and pictorial appearance of the Agreement, will have the same effect as physical delivery of the paper document bearing the original signature.

SIGNATURES BEGIN ON THE NEXT PAGE

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

Lane, Cliff (NIH/NIAID) [E] Digitally signed by Lane, Cliff (NIH/NIAID) [E]
Date: 2020.07.25 15:58:42 -04'00'

25 July 2020

(Signature) (Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6)

Digitally signed by (b)(6)
DN: cn=(b)(6) o=Eli Lilly and Company, ou=Trial Capabilities, email=(b)(6) @lilly.com, c=US
Date: 2020.07.25 14:52:05 -04'00'

25 July 2020

(Signature) (Date)

(b)(6)
(b)(6)

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

cc: Principal Investigators, Clinical Research Sites

Product Research & Development

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CQD PRD Approver - (b)(6) - 2020-07-25T13:54:50
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Appendix 1

Quality Procedures

1. General Information

Eli Lilly and Company (Product Research and Development) (hereafter referred to as "**LILLY**") and The National Institute of Allergy and Infectious Diseases (hereafter referred to "**NIAID** ") have entered into a Clinical Trial Agreement for the supply of product(s) for use in clinical trial(s). As indicated in the Clinical Trial Agreement, the Division of Clinical Research (DCR) has delegated a portion of the sponsor responsibilities to the University of Minnesota. The intent of this appendix to the Clinical Trial Agreement is to define the quality roles and responsibilities and to establish, clarify, and communicate the quality expectations for activities performed by LILLY and NIAID.

2. Definitions

The definitions listed below apply to this Quality Procedure.

AoR: Acknowledgment of Receipt

ASM: Animal Sourced Material.

Change: A planned alteration, replacement, origination of a new item (e.g., product, equipment, facility) or elimination of specifications, methods, facilities, utilities, equipment, computer systems, master records or controls that are used for the manufacture, processing, packaging or holding of PRODUCT or printed PRODUCT to ensure it meets all of its quality requirements.

cGMP: Current standards of good manufacturing practice, as amended from time to time, related to the manufacture of Product as set forth in the European Commission Directive 2003/94/EC, Eudralex Volume 4 and FDA CFR Parts 11, 210, 211 and United States Code of Federal Regulations and are required by the Food and Drug Administration (FDA) or other Regulatory Authorities (as defined herein), as applicable.

CoA: Certificate of Analysis

CT: Acronym for Clinical Trial.

CTA: Clinical Trial Application

Deviation: A departure from an approved instruction or established standard.

Distribution Complaint: A notification from an external party resulting from a distribution related issue (e.g., quantity discrepancy, wrong item, damage, etc.) identified by the recipient of the distributed Material.

Drug Product (DP): Any product that has completed all processing stages up to, but not including, final packaging.

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Finished Product: A drug product that has undergone all stages of manufacture, including packaging, in its final container and labeling.

Good Distribution Practices (GDP): That part of quality assurance which ensures products are consistently stored, transported, and handled under suitable condition as required by the marketing authorization or product specification.

IMPD: Investigational Medicinal Product Dossier

Product: A Finished Product, Drug Product, active ingredient, inactive raw material, key intermediates, test article, or cell bank unless stated otherwise. As used in this Procedure, PRODUCT refers to the list identified in Section 5 of this Appendix.

Product Complaint: Any written, electronic, or oral communication that states possible deficiencies in the Study Product that may involve failure to meet any of its specifications (e.g., identity, quality, purity, durability or reliability), including its labeling or package integrity. A Product Complaint may have an impact on the safety and efficacy of the Study Product.

PSF: Product Specification File

Qualified Person (QP): Legally defined person responsible to release each batch of product sold or used in a clinical trial in the EU.

Recalls: Removal or correction of a marketed product that regulatory agencies (e.g., the Food and Drug Administration) considers to be in violation of the laws it administers and against which the agency would initiate legal action (e.g., seizure. Recall does not include a market withdrawal or a stock recovery).

Reprocessing: Introducing an intermediate, API, or drug product, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process.

Retrievals: A process whereby clinical supplies, previously released for use in a clinical trial, but which have since been found to be or are suspected of being compromised with respect to product quality, are identified, located, and brought back under the control of clinical trial sponsor.

Rework: Subjecting an intermediate, API, or drug product that does not conform to standards or specification to one or more processing steps that are different from the established, routine manufacturing process to obtain intermediate, API, or drug product (e.g., recrystallizing with a different solvent) of acceptable quality.

Secondary Packaging: Packaging components that are not and will not be in direct contact with the drug product.

Significant: As used in this Procedure, “Significant” is understood as anything having the potential to affect safety, identity, strength, purity, or quality.

TSE/BSE: Acronym for Transmissible Spongiform Encephalopathy/Bovine Spongiform Encephalopathy.

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3. General Responsibilities

	Item	LILLY	NIAID
	General Quality		
3.1.	Acknowledge the terms of this Quality Procedure and subsequent amendments are communicated to the relevant staff, as applicable.	X	X
3.2.	Acknowledge that systems are in place to maintain compliance with all current standards of Good Manufacturing Practices (cGMP) as specified in European Commission Directive 2003/94/EC, Eudralex Volume 4, including Annex 13 and FDA 21 CFR Parts 11, 210, 211 and ICH Q7 as applicable.	X	X
3.3.	Acknowledge that all licenses, authorizations and approvals required by Applicable Laws and Regulations are obtained and maintained in order to process, store, ship, destroy, Investigational Medicinal Product, in accordance with the Clinical Trial Applications.	X	X
3.4.	Prepare and submit the IMPD in the different countries and provide confirmation of approval by competent authorities. Prepare and submit the QP declaration for non-EU sites, as applicable.	X	
3.5.	Study Sponsor		X
	Manufacturing/Packaging/Labeling		
3.6.	Responsible for manufacture, testing and GMP release of the PRODUCT and FINISHED PRODUCT (including CT investigational labeling) against the corresponding IND/IMPD Authorization including applicable requirements specified in the FDA cGMP (21 CFR 210-211), the EC guide to Good Manufacturing Practices (2003/94/EC), Regulatory Filing, and ICH Q7 for API, as well as all laws, regulations, guidelines.	X	
3.7.	Responsible to maintain the Competent Authority license(s) for sites responsible for manufacture and release of the PRODUCT.	X	
3.8.	Shall develop PRODUCT labeling that is compliant with 21 CFR 312.6 and is responsible for approving the CT investigational label text.	X	
3.9.	Will store reference and retain samples in accordance with internal procedures	X	
3.10.	Will develop and maintain the PSF and associated Batch Manufacturing Records.	X	
3.11.	Shall be responsible for the final quality and regulatory release for clinical use of the PRODUCT prior to providing to NIAID for distribution to sites.	X	
3.12.	Perform QP certification of PRODUCT confirming compliance with: • GMPs • PSF • Regulatory dossiers as approved by the local authorities (CTA). And provide batch release documentation (QP certification, CoA, importation), as applicable.	X	
3.13.	Will not rework or reprocess the PRODUCT		X

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3. General Responsibilities

	Item	LILLY	NIAID
	Distribution		
3.14.	Request and provide • License(s) for each hub (distribution center) prior to first shipment and license updates as applicable • Competent Authority (CA) approval and Ethical Committee approval prior to the first shipment showing the readiness to receive Clinical Trial shipments		**X**
3.15.	PRODUCT will be shipped under appropriate conditions with temperature monitoring devices (if applicable) and is responsible for the PRODUCT through delivery and receipt by **NIAID**, this includes investigation of distribution complaints per local procedures and temperature excursion alarms.	**X**	
3.16.	Request for all subsequent PRODUCT shipments through delivery and receipt at clinical sites.		**X**
3.17.	Shall request for the final quality and regulatory release for clinical use of the PRODUCT prior to providing to clinical investigator sites.		**X**
3.18.	Shall request handle and store PRODUCT(s) according to product specific transport and storage conditions provided by LILLY		**X**
3.19.	Shall request to follow GDPs when supplying PRODUCT(s) to clinical investigators.		**X**
3.20.	Request for the investigation of any temperature excursions after receipt of PRODUCT. When requested, LILLY will provide PRODUCT disposition for these temperature excursions.		**X**
3.21.	Will request no dating extensions are performed by the site on the PRODUCT		**X**
3.22.	Shall request PRODUCT is not utilized in the clinical trial after it has exceeded its expiry date.		**X**
	Drug Accountability, Returns and Destructions		
3.23.	Responsible for requesting drug accountability processes are in place at the clinical sites.		**X**
3.24.	Will request there is no redistribution between sites		**X**
3.25.	Request for the reconciliation and destruction of unused or expired PRODUCT. Certificates of destruction may be requested at the close of the trial.		**X**
3.26.	Return of PRODUCT will not be allowed after acceptance unless in a manner consistent with the Clinical Trial Agreement.		**X**

	Item	LILLY	NIAID
	Product Complaints		
3.27.	Each party shall inform the other party within 2 days if problems and/or defects associated with the PRODUCT, services, or test results have been confirmed to have an impact on the PRODUCT's safety, identity, strength, potency, or quality after transfer of PRODUCT to enable both parties to comply with applicable regulatory reporting requirements, including, but not limited to quality issues, deviations, or discrepancies.	**X**	**X**
3.28.	Shall provide notification in a manner consistent with the Clinical Trial Agreement for product complaints and/or adverse events that require a supplier investigation		**X**
3.29.	Will complete investigations of product complaints in accordance with internal standard operating procedures. A product complaint investigation reference number and high-level summary of the completed complaint investigation will be provided to **NIAID**.	**X**	
3.30.	Responsible for requesting the investigation of product complaints directly related to any subsequent distribution of the PRODUCT.		**X**
	Recalls and Withdrawals		
3.31.	Responsible for notification of product recalls related to the PRODUCT batches supplied within one (1) business day.	**X**	
3.32.	Responsible for requesting notification of any quality issue that could potentially result in PRODUCT retrieval in a manner consistent with the Clinical Trial Agreement.		**X**
3.33.	In the event of a recall of PRODUCT supplied under this Procedure, no public statement may be made as to the cause of, or responsibility for such recall without being consistent with confidentiality protections of the Clinical Trial Agreement.		**X**
	Regulatory and other items		
3.34.	Shall notify within 3 business day(s) of any regulatory or cGMP violations (e.g., FDA Warning Letter; Critical Observation Reported by a US, European or other Health Authority) identified during cGMP inspections and directly impacting the quality of the PRODUCT supplied under this Procedure.	**X**	
4.37	Both parties understand to notify the other party of regulatory investigations relating to the study and/or the PRODUCT supplied under this Procedure.	**X**	**X**

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4. Documentation Requirements

The following documents will be provided by **LILLY** to **NIAID** for each PRODUCT item:

- MSDS
- Letters of Cross Reference and/or country submission documentation
- The Qualified Person's Declaration equivalence to EU GMP, as applicable
- Other documentation, as required, to meet the requirements of the Drug Supply Chain Securities Act (DSCSA).

The following documents will be provided by **LILLY** to **NIAID** for each lot of PRODUCT:

- Certificate of Analysis (CoA) signed by the Quality Unit
- Certificate of GMP Conformance (CoC) signed by the LILLY Quality Unit or QP Release Certificate signed by a LILLY Qualified Person QP Certificate signed by Lilly Qualified Person
- BSE/TSE Certification

The following documents will be provided on behalf of **NIAID** to **LILLY**:

- Copy of CTA approval
- Approval letters of the study by the Regulatory Authorities including comments if any.
- License(s) for each hub prior to first shipment and license updates as applicable

5. Applicable Products

Lilly Code/Identifier	Material Name	Dosage Form
LY3819253	LA846 (LY-COV-555)	700mg Vial

Date Printed: 2020-07-25T14:04:38

Version 0 is Effective as of 2020-07-25T14:02:29

6. Responsible Parties and Quality Contact List

LILLY Contacts

Contact Name	e-Mail/Phone Number	Role/Responsibility
(b)(6) – Clinical Trials (b)(6)	(b)(6)@lilly.com Group Distribution Email: CT_QA_External_Partners@lilly.com	**Primary Quality Contact** for issues including material issues found during receipt or packaging
Consumer Product Quality Assurance – Americas Regional Center (Complaint Management Group)	Group Distribution Email: US_CPQA@lilly.com	**Product Quality Complaints**
(b)(6) Consultant – QA Global Development Operations	(b)(6)@lilly.com (b)(6)	**Product Retrievals**
(b)(6) (b)(6) (b)(6)	(b)(6)@lilly.com (b)(6) Group E-mail: ELECTS_QP@lists.lilly.com	**QP Support**

NIAID Quality Contacts

Contact Name	e-Mail/Phone Number
Laura A. McNay, MS Deputy Director for Operations and Management, Division of Clinical Research, NIAID, NIH	Office Phone (b)(6) Email: (b)(6)@niaid.nih.gov

7. Acknowledgments

Acknowledgment signatures indicates that you have reviewed this document and that you acknowledge the procedure contained in this document.

LILLY Acknowledgments

Refer to the electronic acknowledgment signatures managed in LILLY's electronic document management system (EDMS).

Name	Title
(b)(6)	(b)(6)
(b)(6)	(b)(6)

NIAID Acknowledgment

Name	Title	Signature	Date
Laura A. McNay	Deputy Director for Operations and Management, Division of Clinical Research, NIAID, NIH	(b)(6)	7/26/2020

8. Revision History

Rev No#	Author	Approval Date	Changes
00	(b)(6)	See EDMS	New Document

Version 0 is Effective as of 2020-07-25T14:02:29 Date Printed: 2020-07-25T14:04:38

AMENDMENT NO. 1
TO
CLINICAL TRIAL AGREEMENT

This 1st Amendment (NIAID Ref. No. 2020-0919-1) to Clinical Trial Agreement (NIAID Ref. No. 2020-0919) is made as of the date of the last authorized signature by and between Eli Lilly and Company (the "Company") and The National Institute of Allergy and Infectious Diseases ("NIAID"), an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the Division of Clinical Research ("DCR"). Each of Company and NIAID may be referred to herein as a "Party" or together as "Parties."

WHEREAS, Company and NIAID entered into a Clinical Trial Agreement, dated July 25, 2020 (the "Agreement") for the conduct of the clinical trial designated as Protocol ACTIV3/INSIGHT014, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)" ; and

WHEREAS, the Parties desire to amend the Agreement as set forth herein;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, and intending to be legally bound, the Parties hereto agree as follows:

1. Definitions. All terms used in this Amendment and not otherwise defined herein shall have the same meanings ascribed to them in the Agreement.

2. Amendments:

   a. The following Section 11.8 is hereby added to the Agreement:

      11.8. NIAID (DCR) will provide to the Company Chief Medical Officer, Chief Scientific Officer, Vice President of Safety, VP of Development for COVID-19 therapies, and Dr. Lei Shen a copy of the unblinded DSMB report reviewed by the DSMB on October 13, 2020. This information will be held under the strictest of confidentiality by those individuals.

3. All other terms and conditions of the Agreement shall remain unchanged.

SIGNATURES BEGIN ON NEXT PAGE

IN WITNESS WHEREOF, each Party has caused this This 1st Amendment (NIAID Ref. No. 2020-0919-1) to Clinical Trial Agreement (NIAID Ref. No. 2020-0919) to be executed by its authorized representative.

ACCEPTED AND AGREED TO:

(b)(6)

10/14/2020

(Signature) (Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6)

(b)(6)
cn=(b)(6) o=Eli Lilly and Company, ou=Trial Capabilities, email=(b)(6)@lilly.com, c=US
2020.10.14 14:31:55 -04'00'

(Signature) (Date)

(b)(6)
(b)(6)

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

cc: Principal Investigators, Clinical Research Sites

AMENDMENT NO. 2
TO
CLINICAL TRIAL AGREEMENT

This 2nd Amendment (NIAID Ref. No. 2020-0919-2) to Clinical Trial Agreement (NIAID Ref. No. 2020-0919) is made as of the date of the last authorized signature by and between Eli Lilly and Company (the "Company") and The National Institute of Allergy and Infectious Diseases ("NIAID"), an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the Division of Clinical Research ("DCR"). Each of Company and NIAID may be referred to herein as a "Party" or together as "Parties."

WHEREAS, Company and NIAID entered into a Clinical Trial Agreement, dated July 25, 2020 (the "Agreement") for the conduct of the clinical trial designated as Protocol ACTIV3/INSIGHT014, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)", as amended on October 14, 2020 ; and

WHEREAS, the Parties desire to amend the Agreement as set forth herein;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, and intending to be legally bound, the Parties hereto agree as follows:

1. Definitions. All terms used in this Amendment and not otherwise defined herein shall have the same meanings ascribed to them in the Agreement.

2. Section 11.7 is deleted in its entirety and is replaced with the following:

    11.7. Company will be responsible for preparing the final Clinical Study Report in accordance with ICH E3, "Structure and Content of Clinical Study Reports" and will provide a copy of the Clinical Study Report to NIAID (DCR) and the SDMC for review and comment prior to its finalization.

3. All other terms and conditions of the Agreement shall remain unchanged.

SIGNATURES BEGIN ON NEXT PAGE

IN WITNESS WHEREOF, each Party has caused this This 2nd Amendment (NIAID Ref. No. 2020-0919-2) to Clinical Trial Agreement (NIAID Ref. No. 2020-0919) to be executed by its authorized representative.

ACCEPTED AND AGREED TO:

(b)(6)

(Signature)

11/13/2020

(Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6)

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cn=(b)(6) o=Eli Lilly and Company, ou=Trial Capabilities, email=(b)(6) @lilly.com, c=US
2020.11.09 14:14:32 -05'00'

(Signature)

9 November 2020

(Date)

(b)(6)
(b)(6)

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

cc: Principal Investigators, Clinical Research Sites

CONFIDENTIAL DISCLOSURE AGREEMENT

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, National Institute of Allergy and Infectious Diseases ("NIAID"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS") and AstraZeneca Pharmaceuticals LP ("AstraZeneca") (each a "Party" and collectively, the "Parties"), intending to be legally bound as of the date of the last signature hereto ("Effective Date"), agree that:

1. A Party ("Disclosing Party") may disclose information to the other ("Receiving Party") for the purpose of discussing a proposed collaboration on AstraZeneca's anti-SARS-CoV-2 monoclonal antibody cocktail AZD7442 for treatment of SARS CoV-2 ("Purpose"). The Disclosing Parties are: NIAID and AstraZenenca.

2. The information disclosed under this Agreement ("Confidential Information") is described as: any and all information associated with AstraZeneca's anti-SARS-CoV-2 monoclonal antibody cocktail AZD7442.

3. The Receiving Party will not disclose the Confidential Information of the Disclosing Party to any person except its employees, investigators from the AIDS Clinical Trials Group (ACTG), International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Cardiothoracic Surgical Trials Network (CTSN), Prevention and Early Treatment of Acute Lung Injury (PETAL), employees of National Heart, Lung, and Blood Institute (NHLBI) involved in the oversight and management of CTSN and PETAL, employees of the Foundation for the National Institutes of Health (FNIH) involved the ACTIV program, and the U.S. Department of Veterans Affairs (VA), consultants or contractors to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information.

4. The Receiving Party's duties under this Agreement shall apply to any Confidential Information shared orally or in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked "Confidential." Oral disclosures must be reduced to writing, marked "Confidential" and sent to the Receiving Party's representative designated in Paragraph 9 within thirty (30) days after disclosure to be considered Confidential Information.

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public

domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure in the possession of the Receiving Party; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party, without reference to the information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return all Confidential Information received, except that the Receiving Party may retain in its confidential files one (1) copy of written Confidential Information for record purposes only.

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required to disclose any of the Confidential Information, the Receiving Party shall provide the Disclosing Party with timely notice and, to the extent practicable, consult with the Disclosing Party prior to any disclosure.

8. This Agreement is made under and shall be construed in accordance with Federal laws as applied by the Federal Courts in the District of Columbia, and constitutes the entire understanding between the Parties with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for three (3) years from the Effective Date.

9. Notices or other communications required to be sent to NIAID under this Agreement shall be sent in writing and addressed to Wade Green, Technology Transfer & Intellectual Property Office, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Ste 6D Rockville, MD 20852, email: (b)(6) @niaid.nih.gov. Notices required to be sent to AstraZeneca under this Agreement shall be in writing by email and addressed to (b)(6) (b)(6) BioPharceuticals R&D, (b)(6) @astrazeneca.com.

10. Each Party has caused this Agreement to be executed on its behalf in duplicate (each of which duplicate shall be deemed to be an original).

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Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Institute of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH)
5601 Fishers Lane, Ste 6D
Rockville, MD 20852

Authorized Signature:

Wade W. Green -S Digitally signed by Wade W. Green -S
Date: 2020.07.30 14:10:02 -04'00'

Wade Green, Ph.D.
Lead Technology Transfer & Patent Specialist
Technology Transfer & Intellectual Property Office, NIAID

Date (Month/Day/Year): 30 July 2020

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19803
Authorized Signature:

(b)(6)

Name: (b)(6)
Title: Head of Transactions, Business Development
BioPharmaceuticals R&D

Date (Month/Day/Year): 30 July 2020

IND SPONSOR: NIAID (DAIDS)

CLINICAL TRIAL AGREEMENT

BETWEEN

DIVISION OF AIDS (DAIDS), NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

&

ASTRAZENECA PHARMACEUTICALS LP

Based on

Protocol ACTIV-2/A5401

Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)

The **National Institute of Allergy and Infectious Diseases** ("**NIAID**"), an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services (HHS), as represented by the **Division of AIDS** ("**DAIDS**") and **AstraZeneca Pharmaceuticals LP** ("**Company**"), located at 1800 Concord Pike, Wilmington, DE 19803, (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial designated as Protocol **ACTIV-2/A5401**, entitled "**Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)**."

This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). NIAID (DAIDS) will conduct this Clinical Trial through NIAID (DAIDS) extramurally funded AIDS Clinical Trials Group (ACTG) Clinical Research Sites under the terms of their Grant/Cooperative Agreement with NIAID (DAIDS). In the event that non-ACTG Clinical Research Sites funded by NIAID (DAIDS) are included in this Clinical Trial in order to complete enrollment, these sites will meet NIAID (DAIDS) standards for clinical research sites conducting research sponsored by NIAID (DAIDS). The Clinical Research Sites and their respective Investigators are not parties to this Agreement.

This Agreement sets forth the terms and conditions under which this Clinical Trial will be conducted and managed.

Company and NIAID (DAIDS) agree as follows:

1. DEFINITIONS

The terms listed in this Section will carry the meanings indicated throughout this Agreement. To the extent that a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code ("U.S.C.") or the Code of Federal Regulations ("C.F.R."), the definition in the U.S.C. or C.F.R. will control.

"**ACTG**" means the AIDS Clinical Trials Group network sponsored and funded by NIAID (DAIDS) in accordance with the terms of a Cooperative Agreement.

"**Adverse Event**" or "**AE**" will be defined per the Protocol.

"**Affiliate**" means, with respect to Company, (i) any legal entity of which the securities or other ownership interests representing fifty percent (50%) or more of the equity or fifty percent (50%) or more of the ordinary voting power or fifty percent (50%) or more of the general partnership interest are, at the time such determination is being made, owned, controlled or held, directly or indirectly, by such legal entity; or (ii) any legal entity which, at the time such determination is being made, is controlling or under common control with, such legal entity. As used herein, the term "control," whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract or otherwise.

"**Agreement**" means this Clinical Trial Agreement ("**CTA**"), all executed amendments and supplements to this Agreement, and all schedules, appendices and/or addenda to this Agreement.

"**Case Report Form**" or "**CRF**" means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Clinical Research Sites**" means the clinical research sites designated as the ACTG sites and any other sites where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Trial**" means a biomedical or behavioral research study of Human Subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, or devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. In this Agreement, Clinical Trial means the clinical trial for the Protocol.

"**Confidential Information**" means confidential scientific, proprietary, business and/or financial information, provided that Confidential Information does not include:

(a) Information that is in the public domain or subsequently enters the public domain through no fault of the receiving Party or its representatives;

(b) Information that is presently known or becomes known to the receiving Party from its own independent sources, without restriction as to confidentiality or use, from a person having the legal right to disclose the data;

(c) Information that can be established by competent proof was already known and lawfully in the possession of the receiving Party at the time of the disclosure, without restriction as to confidentiality or use;

(d) Information that is independently created or compiled by the receiving Party without reference to or use of the Confidential Information and such independent development can be documented by receiving Party with written records;

(e) Subject in each case to the provisions in this Agreement set forth in Section 12 (Publication and Press Releases) of this Agreement, information that is reasonably required by scientific standards for publication of the results of the Clinical Trial (including Clinical Trial methods and/or data) or any information that is necessary for other researchers to verify the results of the Clinical Trial;

(f) Information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Study Product; or

(g) Information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, or required to be disclosed by a court of competent jurisdiction or governmental authority, provided that the Party required to disclose provides the other Party with prompt written notice and an opportunity (if legally permissible) to obtain a protective order.

"**Critical Event**" means any unanticipated study-related incident that is likely to cause or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity.

"**Data and Safety Monitoring Board**" or "**DSMB**" means an independent group of experts that advises NIAID (DAIDS) and the Investigators. The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (2) make recommendations to NIAID (DAIDS) concerning the continuation, modification, or termination of the Clinical Trial.

"**Distributor**" means the NIAID (DAIDS) contractor who will be distributing the Study Product to the Clinical Research Sites. The Distributor for this Clinical Trial is the Clinical Research Products Management Center ("**CRPMC**").

"**Effective Date**" means the date of the last signature of the Parties executing this Agreement.

"**Electronic Common Technical Document**" or "**eCTD**" means the standard format for electronic regulatory submissions as per 21 U.S.C. § 379k-1, "Electronic Format for Submissions," and as further described in FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," 80 Federal Register 26057 (2015).

"**FDA**" means the U.S. Food and Drug Administration.

"**Government**" means the Federal Government of the United States of America.

"**Grant/Cooperative Agreement**" means the award providing financial assistance from NIAID (DAIDS) for approved activities. In a Grant, performance responsibility rests primarily with a grantee with little or no government involvement in the research. A NIAID (DAIDS) Cooperative Agreement is a Grant in the U series that features substantial NIAID (DAIDS) scientific involvement.

"**Health Authority**" **or** "**HA**" means any non-U.S. Health Authority used when the Clinical Trial is being conducted in whole or in part at a non-U.S. Clinical Research Site requiring the use of non-U.S. regulatory agencies.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. § 46.102(e)(1), a living individual about whom an Investigator conducting research:

(a) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimen; or

(b) Obtains, uses, studies, analyzes or generates Identifiable Private Information or identifiable biospecimens.

"**ICH**" means the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Cited are:

ICH E3: "Structure and Content of Clinical Study Reports."

ICH E6: "Good Clinical Practice: Consolidated Guidance," published in the Federal Register [83 Federal Register 8882 (2018)]. Also referred to as "FDA Good Clinical Practice Guidelines."

"**Identifiable Private Information**" or "**IPI**" about a Human Subject means private information from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**IND**" means an "**Investigational New Drug Application**," filed in accordance with 21 C.F.R. Part 312, under which clinical investigation of an experimental drug or biologic (Study Product) is performed in Human Subjects in the U.S., or intended to support a U.S. licensing action.

"**Institutional Review Board**" ("**IRB**") or "**Independent Ethics Committee**" ("**IEC**") means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects, and 21 C.F.R. Part 56, Subpart C: IRB Functions and Operations, as amended April 1, 2013, and other applicable regulations, an independent body comprising medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of the Human Subjects involved in a clinical trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**Invention**" means any invention or discovery that is or may be patentable or otherwise protectable under Title 35 of the U.S.C.

"**Investigator**" means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Study Product to a Human Subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, Investigator means the individual(s) identified as responsible for the conduct of the Clinical Trial at any of the designated ACTG participating Clinical Research Sites.

"**Investigator's Brochure**" or "**IB**" means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Study Product, including animal screening, preclinical toxicology and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the Study Product or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Study Product.

"**Manufacturing Know-How**" means Company's proprietary information about the facilities, processes or articles used in the manufacturing, processing and packaging of

the Study Product.

"**Office for Human Research Protections**" or "**OHRP**" means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"**Patent**" means any issued U.S. patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

"**PPD**" means Pharmaceutical Product Development, Inc., a contract research organization responsible for monitoring the Clinical Trial, under contract to NIAID (DAIDS).

"**Protected Health Information**" or "**PHI**," as defined in 45 C.F.R. Parts 160 and 164, under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), includes any *individually identifiable* health information. *Identifiable* refers not only to data that is explicitly linked to a particular individual; it also includes health information with data items which reasonably could be expected to allow individual identification.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV-2/A5401, "Adaptive Platform Treatment Trial for Outpatients with COVID-19 (Adapt Out COVID)." The Protocol describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. The Agreement will be governed by the most recent version of the Protocol, and should the Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement, the terms of the Agreement will govern.

"**Protocol Team**" means the team responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. The Protocol Team will include the protocol chair (an Investigator), representatives from Company, other Investigators, representatives from NIAID (DAIDS), and the persons involved with statistical and data analysis for the Clinical Trial. Participation on the Protocol Team will be as agreed by the Parties and will take into account any special requirements of the Protocol design.

"**Regulatory Support Center**" or "**RSC**" means the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory activities related to NIAID (DAIDS)'s clinical research. The RSC is part of Technical Resources International, Inc. (TRI), and operates pursuant to a contract between TRI and NIAID (DAIDS).

"**Regulatory Application**" or "**RA**" means an IND-equivalent, non-U.S. Regulatory Application, applicable when the Clinical Trial is being conducted in whole or in part at a non-U.S. clinical research site.

"**Sponsor**" means, in accordance with the definition in 21 C.F.R. § 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with Study Product. For the purposes of this Agreement, "Sponsor" is referred to as the IND holder.

"**Statistical and Data Management Center**" or "**SDMC**" means the organization(s) responsible for providing statistical and data management services for the Clinical Trial that is the subject of this Agreement.

"**Study Product**" means, in accordance with 21 C.F.R. § 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301, *et seq*., Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended. In this Agreement, the anti-SARS-CoV-2 monoclonal antibody cocktail AZD7442 is referred to as the Study Product.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 Company acknowledges that NIAID (DAIDS) funds the Clinical Research Sites under a Grant/Cooperative Agreement, and therefore, the Clinical Research Sites have certain existing contractual or other legal obligations to NIAID (DAIDS).

2.2 Company will not provide any funding or material for any aspect of the Clinical Trial to any Clinical Research Site participating in the Clinical Trial without prior written notification to NIAID (DAIDS). In addition, subject to Section 14.4 of this Agreement, Company will not enter into any separate agreements, including, but not limited to, material transfer agreements, with the Clinical Research Sites or the Investigators at the Clinical Research Sites that interfere with the conduct of this Clinical Trial.

2.3 NIAID (DAIDS) will comply with all applicable U.S. and foreign government, state and local laws, regulations and guidelines in the performance of its obligations hereunder. Without limiting the foregoing, NIAID (DAIDS) hereby certifies that it did not and will not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:

(i) debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or

(ii) suspended by OHRP as a clinical research site under 45 C.F.R. Part 46.; or

(iii) to the extent NIAID (DAIDS) is aware, excluded or otherwise rendered ineligible to participate in federal healthcare programs or federal procurement or non-procurement programs.

2.3.2 Any person convicted of a felony under federal law for conduct:

(i) relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application (NDA), Biologics License Application (BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or

(ii) otherwise relating to the regulation of any drug product or medical device under the FDCA.

2.3.3 Any person performing services in connection with this Clinical Trial who has been disqualified as a clinical investigator under 21 C.F.R. § 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required by 21 C.F.R. § 312.53.

2.4 If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party immediately.

2.5 Per Grant/Cooperative Agreement or other agreement, NIAID (DAIDS) requires that the Investigators at Clinical Research Sites conduct the Clinical Trial in accordance with applicable provisions of ICH E6: FDA Good Clinical Practice Guidelines, and requires that they comply with all applicable U.S., foreign government, state and local laws, regulations and guidelines.

2.6 Company agrees that this Protocol will be conducted only at sites as defined in the Protocol. However, Company can conduct, at its own expense and under its own IND/RA, additional clinical trials with the Study Product, at non-NIAID (DAIDS) funded sites. Company agrees to inform NIAID (DAIDS) in writing of any other clinical trials it may support for the use of the Study Product that would compete with this Clinical Trial for the same Human Subject population.

2.7 If Protocol-specified assays expected to be included in a regulatory submission are performed in laboratories not monitored by NIAID (DAIDS), Company warrants that such laboratories will comply with Good Clinical Laboratory Practice (GCLP) and all applicable regulatory requirements. Company will provide NIAID (DAIDS) with results of such assays and, upon request, provide documentation to support that the testing and laboratory operations are compliant with GCLP and all applicable regulatory requirements. NIAID (DAIDS), through its contractor, may audit the laboratory(ies) to ensure compliance with GCLP and all applicable regulatory requirements.

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND.** NIAID (DAIDS) will submit an IND covering the Protocol to the FDA. The IND will satisfy all of the requirements of the FDA, and, as applicable, will comply with

eCTD format requirements. Company agrees to provide all requested documents to NIAID (DAIDS) in eCTD format. Company will provide a letter granting the FDA permission to cross-reference Company's pertinent Master File (MF), New Drug Application (NDA), Biologics License Application (BLA), and/or INDs in support of the NIAID (DAIDS)'s IND, and in return, NIAID (DAIDS) will also provide a letter to Company, if requested, granting the FDA permission to cross-reference the IND filed by NIAID (DAIDS) for this Clinical Trial. NIAID (DAIDS) will provide a copy of all IND submissions to Company at the time they are submitted to the FDA. Any Confidential Information of another party will be removed. If applicable, NIAID (DAIDS) will verify that each RA was submitted to the relevant HA according to applicable laws, rules, regulations and guidelines.

3.2 NIAID (DAIDS) may delegate regulatory obligations to one or more third parties to facilitate NIAID (DAIDS)'s oversight, monitoring and administration of the Clinical Trial at Clinical Research Sites outside of the United States. NIAID (DAIDS)'s third party delegate(s) will submit any clinical trial application and subsequent reports to all applicable regulatory authorities outside of the United States and will provide timely and accurate information on its activities to (NIAID) DAIDS to enable the exercise of its role as Sponsor.

3.3 NIAID (DAIDS) shall ensure that, where Manufacturing Know-How is required to be disclosed in full to support an RA, such Manufacturing Know-How that is marked as "Confidential Information" shall be kept confidential consistent with Section 13 of this Agreement. Company shall not disclose Manufacturing Know-How to NIAID (DAIDS), unless specifically requested by NIAID (DAIDS).

3.4 **Clinical Research Site Monitoring.** NIAID (DAIDS), through PPD, will be responsible for Clinical Research Site monitoring in accordance with the clinical monitoring plan. Monitoring will be done in compliance with applicable provisions of the FDA/HA regulations. NIAID (DAIDS) will communicate any Critical Event findings from clinical monitors to Company in a timely manner.

3.5 **Quality Audits**. If required by the FDA and upon reasonable notice, Company may perform quality site audit visits and will coordinate those visits with NIAID (DAIDS) and the relevant Clinical Research Site staff.

3.6 **Adverse Event Reporting.**

3.6.1 NIAID (DAIDS) will collect AE reports according to the procedures outlined in the Protocol and in accordance with 21 C.F.R. § 312.32. The Clinical Research Sites will report AEs to NIAID (DAIDS) in a timely manner, in accordance with the procedures outlined in the Protocol and in accordance with 21 C.F.R. § 312.32. NIAID (DAIDS) will assume responsibility for the reporting of AEs to the FDA and will provide copies of all of the safety reports to Company. NIAID (DAIDS) will verify that safety reports relating to the RAs were made to the HAs

in accordance with applicable laws, rules, regulations, guidelines and the Protocol. Such reports will be sent to:

AstraZeneca Patient Safety (Pharmacovigilance)
AstraZeneca Pharmaceuticals LP
1800 Concord Pike, Wilmington, DE 190803
E-mail: AEMailboxClinicalTrialTCS@astrazeneca.com.

3.6.2 NIAID (DAIDS) will report all unexpected Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the FDA and Company on a timely basis consistent with 21 C.F.R. § 312.32 and the Protocol. NIAID (DAIDS) will report other serious and non-serious AEs to the FDA and to Company on a timely basis consistent with 21 C.F.R. § 312.33 and the Protocol. NIAID (DAIDS) will report all SAEs associated with the Study Product observed in this Clinical Trial to Company at the address listed in Section 3.6.1 above within five (5) business days of PPD receiving the SAE report, and will provide follow up information to Company at the time that any follow up safety report may be submitted to the FDA. The reporting will be completed in the timeframes consistent with 21 CFR 312.32. NIAID (DAIDS) will verify that such event reporting related to the RAs is reported to the HAs in accordance with applicable laws, rules, regulations, guidelines and the Protocol.

3.6.3 Company agrees not to contact the Clinical Research Sites directly for information related to AEs. Company shall contact PPD for information related to SAEs at all of the following:

PPD Oversight Contact
(b)(6) Project Management
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

PPD PVG Contact
(b)(6) PVG Manager
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

As the manufacturer, Company will, in a timely manner consistent with FDA/HA requirements and during the term of this Clinical Trial, provide NIAID (DAIDS) with any information it now has or may obtain in the future regarding the safety and/or the toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial. NIAID (DAIDS) will promptly transmit that information to all Investigators. Such information shall be sent to all of the following:

(b)(6)
Project Manager

PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

(b)(6)
PVG Manager
PPD
E-mail: (b)(6) @ppdi.com
Phone: (b)(6)

Open label/blinded safety reports and unblinded safety reports:
PVGNIAIDACTIV2@ppdi.com

3.7 During the course of the study, if Company is requested by a regulatory agency to unblind an SAE report, NIAID (DAIDS) will collaborate with Company to determine whether the report can be unblinded without undermining the scientific integrity of the Clinical Trial. NIAID (DAIDS) will provide the blinding codes for study subjects randomized to the Study Product or the placebo to the Study Product to Company when all data forms have been keyed into the database for all subjects, data cleaning has been completed and the Protocol Team has declared the study data set to be complete.

3.8 **Pregnancy Reporting.** NIAID (DAIDS) will report pregnancies with respect to the Study Product no later than thirty (30) days of becoming aware of such events. Such reports shall be sent to Company at AEMailboxclinicaltrialTCS@astrazeneca.com.

4. SAFETY MONITORING

Data and Safety Monitoring Board (DSMB). A NIAID (DAIDS) DSMB will monitor this Clinical Trial as described in the Protocol. NIAID (DAIDS) will notify Company in advance of any DSMB review. NIAID (DAIDS) will provide recommendations derived from the DSMB to Company. Prior to the completion of the Clinical Trial, closed DSMB data and reports prepared for DSMB review will be used only for the purposes of the DSMB meeting and will be held in confidence by the DSMB. Open DSMB reports will be shared with the Protocol Team.

5. FDA/HA MEETINGS/COMMUNICATIONS

5.1. With respect to any discussions with the FDA involving data obtained from this Clinical Trial under NIAID (DAIDS)'s IND, NIAID (DAIDS), in consultation with Company, will take the initiative in arranging meetings or conference calls with the FDA. For any discussion with an HA involving the Study Product in the Clinical Trial, Company will have the right to arrange meetings or conference calls with the HA. Formal meetings with the FDA and/or any HA concerning the Clinical Trial design and/or data will be discussed and agreed upon in advance by Company and NIAID (DAIDS). Company will have the right to participate in all formal meetings with the FDA and or any HA. Company agrees not to contact the FDA and/or any HA independently of NIAID

(DAIDS) concerning this Clinical Trial. However, Company may contact the FDA and/or any HA on separate product-related issues. NIAID (DAIDS) will provide Company with copies of all transmittal letters for IND submissions, and formal questions and responses that have been submitted to the FDA. Any Confidential Information of another party will be removed.

5.2. Company will promptly notify NIAID (DAIDS) of:

(a) Any FDA/HA correspondence related to the Protocol that is received by Company, or its Affiliates; and

(b) FDA/HA enforcement actions directed toward Company or its Affiliates, including, but not limited to, warning letters, seizures, or recalls; injunctions/consent decrees; rejection of regulatory submissions or withdrawal of approval for a product; and

(c) Criminal investigations; and

(d) Proceedings to debar Company or its Affiliates or individuals employed under a contract to Company and/or its Affiliates.

5.3. Company will also promptly notify NIAID (DAIDS) of any action taken by the FDA/HA regarding manufacturing of the Study Product that would impact the safety of Human Subjects in the Clinical Trial.

6. MANUFACTURE, SUPPLY, DISTRIBUTION AND USE OF STUDY PRODUCT

6.1 **Manufacture.** Company will ensure that the manufacture and/or packing and analysis of the Study Product is in compliance with current Good Manufacturing Practices ("GMP") and the relevant Company submissions. Any proposed use of a contractor by Company for the manufacture and/or packing, analysis or warehousing of the Study Product shall be the responsibility of Company. Company will retain batch documentation in accordance with GMP and applicable law and regulation.

6.2 Sponsor is responsible for the final distribution of the Study Product to a Clinical Research Site after the Clinical Research Site has satisfied the regulatory requirements, including obtaining IRB/IEC approvals, to commence administering the Study Product in the Clinical Trial. If the Study Product will be distributed to Clinical Research Sites within the European Union, release of the Study Product including final Qualified Person Certification (Qualified Person as defined in EEC Directive 2001/83/EC) will be provided by Sponsor. Company shall provide Sponsor with supporting release documents including a Certificate of Conformity and Certificate of Analysis ("CoA"). Where requested, Company shall provide a Qualified Person Confirmation for partially manufactured drug product confirming compliance to Good Manufacturing Practice (GMP) and to the Company IMPD/IND.

6.3 **Supply.** NIAID (DAIDS) shall provide Company with an estimate of the quantity of Study Product that will be required to complete the Protocol. Company will supply the Study Product to NIAID (DAIDS) without charge and in mutually agreed upon quantities and conditions sufficient to complete the Protocol and on a schedule mutually agreed

upon by the Parties to ensure a sufficient supply of unexpired Study Product. Company will be responsible for labeling the Study Product used in the Clinical Trial of U.S. supply. If required, NIAID (DAIDS) will be responsible for affixing an auxiliary label to include any ancillary information that may be necessary.

6.4 **Distribution.**

6.4.1 Company will ship the Study Product to the CRPMC as mutually agreed by the Parties. Company will provide specific storage and/or shipping instructions for the Study Product to NIAID (DAIDS), or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. Company warrants that any packaging for hazardous material, provided by Company, meets Department of Transportation regulatory requirements for use at all Clinical Research Sites.

6.4.2 The Study Product must be received by the CRPMC or Clinical Research Sites in usable condition and accompanied by Material Safety Data Sheet (MSDS), specific storage and shipping instructions, stability and/or expiration dating information, the CoA and the Certificate of Compliance (CoC).

6.4.3 If there is evidence that the Study Product that arrived at the CRPMC or Clinical Research Sites has not been maintained according to the defined shipping instructions, or is potentially adulterated, NIAID (DAIDS) will contact Company to inform it of the condition of the received Study Product and to determine if the Study Product is usable or if it must be replaced. If the Study Product must be replaced, Company will replace it at no cost to NIAID (DAIDS) or the Clinical Research Sites.

6.5 **Use.** NIAID (DAIDS), through the CRPMC, will be responsible for ensuring that the Study Product is distributed to the Clinical Research Sites under appropriate storage conditions specified by Company, such that the quality and integrity of the Study Product is not compromised. NIAID (DAIDS) will not transfer the Study Product to parties other than the CRPMC or the Clinical Research Sites, nor will NIAID (DAIDS) chemically modify, replicate, make derivatives of or reverse engineer the Study Product unless mutually agreed in writing by the Parties. NIAID (DAIDS), pursuant to the Grant/Cooperative Agreement, will ensure that the Investigators: (i) use the Study Product only in accordance with the Protocol and for no other purpose; (ii) do not transfer the Study Product to any parties except Company, the CRPMC or the Clinical Research

Sites; and (iii) do not chemically modify, replicate, make derivatives of or reverse engineer the Study Product unless mutually agreed to, in writing, by the Parties.

6.6 **Study Product Return.** Upon completion of the Protocol, NIAID (DAIDS), through the CRPMC, will destroy any unused Study Product.

6.7 **Warranty.** Company represents and warrants that the Study Product supplied meets the specifications cited in the CoA and CoC provided.

6.8 **Source.**

6.8.1 In the event Company elects to terminate its development of Study Product for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to NIAID (DAIDS) within ninety (90) days of discontinuation then Company will provide NIAID (DAIDS) with Study Product sufficient to complete the Clinical Trial in the manner described in the Protocol.

6.8.2 The Parties also agree that should this Agreement be terminated prior to completion of the Protocol, the Protocol will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol and Company will supply enough Study Product to complete the Protocol

7. INVESTIGATOR'S BROCHURE (IB)

Company will provide a current IB in eCTD format for all applicable components of the Study Product, and any later revisions and addenda to the IB for the Study Product, including a summary of changes (SOC), to NIAID (DAIDS), as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Section 13 (Confidential Information) of this Agreement. Company agrees to provide NIAID (DAIDS) any updated version of the IB, with the SOC, within fifteen (15) days of issuance. Company will send the IB and SOC to PPD to the attention of all of the following: the PPD PVG Contact, (b)(6) PVG Manager, at (b)(6) @ppdi.com, and the PPD Oversight Contact, Angie Greer, Project Management, at (b)(6) @ppdi.com. NIAID (DAIDS), through PPD, will distribute the IB to the Clinical Research Sites. NIAID (DAIDS) will address requests for IBs, including updated versions and SOCs, to:

(b)(6)
(b)(6)
E-mail: (b)(6) @astrazeneca.com

8. PROTOCOL DEVELOPMENT AND REGISTRATION

8.1 The Parties agree that enrollment in the Clinical Trial will not start until the version of the Protocol to be used has been reviewed in advance by Company, accepted by the Protocol Team, approved by the relevant IRB(s)/IEC(s) and NIAID (DAIDS) in writing, submitted to the FDA and/or the relevant HAs, as applicable, and any clinical hold issues have been responded to satisfactorily.

8.2 The Parties agree that any alteration in or amendment to the Protocol must be accepted by the Protocol Team, approved in writing by the relevant IRB(s)/IEC(s) and NIAID (DAIDS), and submitted to the FDA and/or the relevant HAs, as applicable, prior to such alteration or amendment becoming effective.

8.3 **Protocol Registration.** All NIAID (DAIDS)-sponsored network protocols which include the informed consent must meet all federal mandates as well as NIAID (DAIDS) requirements to ensure the welfare of Human Subjects in the Clinical Trial.

Each Clinical Research Site, prior to participating in any NIAID (DAIDS)-sponsored study, must submit its informed consent to the NIAID (DAIDS) Protocol Registration Office, c/o Regulatory Support Center (RSC), Technical Resources International, Inc., 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817. Attached is the latest version of the Protocol Registration Manual (see Addendum I).

9. CASE REPORT FORM DEVELOPMENT

NIAID (DAIDS), through the SDMC, will be responsible for the development and subsequent revisions, if any, of the CRFs with appropriate review and comment by the Protocol Team.

10. HUMAN SUBJECTS PROTECTION

10.1 NIAID (DAIDS) and Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The informed consent of each Human Subject participating in the Clinical Trial at a Clinical Research Site will be obtained prospectively using an informed consent process. The sample informed consent document may be reviewed in advance by Company and shall be approved by NIAID (DAIDS) and all appropriate IRB(s)/IEC(s).

10.2 NIAID (DAIDS) and Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46, Protection of Human Subjects. Therefore:

10.2.1 NIAID (DAIDS) and Company will maintain the confidentiality of IPI, including PHI, collected under the Clinical Trial and protect the privacy of the individual Human Subjects unless disclosure is required by law.

10.2.2 To the extent permitted by the informed consent forms and applicable laws, NIAID (DAIDS) and Company may inspect, but not copy, Human Subjects' medical records that might also include information not directly connected to this Clinical Trial. However, NIAID (DAIDS) and Company agree that this information will remain confidential and will not be used for any purpose other than confirmation of Clinical Trial data or to resolve study-related injury issues.

10.2.3 NIAID (DAIDS) and Company agree that neither Party will use, nor will it allow its contractors to use, IPI for any purpose not stated in the Protocol, without the consent of the other Party and local site IRB/IEC approval unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative. NIAID (DAIDS) will ensure that the Investigators do not use IPI for any purpose not stated in the Protocol and informed consent document without the written consent of both Parties and appropriate IRB/IEC approval, unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative.

10.2.4 NIAID (DAIDS) and Company agree to comply with the determinations of all IRB(s)/IEC(s) overseeing this research.

10.2.5 Biospecimens and data related to biospecimens may be provided to Company, consistent with the Protocol and in accordance with the informed consent form, as available and as mutually agreed to by the Parties. Biospecimens and data related to biospecimens collected or created during and after the Clinical Trial will be coded to mask the identity of the Human Subjects to whom they pertain.

11. DATA COLLECTION, ANALYSIS AND MANAGEMENT

11.1 The Clinical Research Sites will be responsible for gathering the data and submitting it to the SDMC. The Protocol Team, which includes Company representatives, will be responsible for the scientific reporting of the data.

11.2 NIAID (DAIDS), through the SDMC, will have responsibility for the data management: collection, entry and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

11.3 Following review by the DSMB of study data through study day 28 in Phase II of the Clinical Trial and receipt by NIAID (DAIDS) of the DSMB's recommendations concerning graduation or otherwise of the Study Product from Phase II to Phase III evaluation, NIAID (DAIDS) will release the analysis report related to the Study Product and concurrently randomized placebo study arms prepared for DSMB review and associated data ("Phase II Analysis Report") to Company, if specifically requested and

justified by Company. The release of the Phase II Analysis Report to Company is not conditioned upon the graduation of the Study Product. Company agrees to restrict access of the Phase II Analysis Report to a named limited group of Company employees for the limited purposes of: 1) supporting Company's request to modify the design of the Phase III component for the evaluation of Company's Study Product; and 2) Study Product development. To protect the integrity of the ongoing Phase II study and of the Phase III study (if Phase III evaluation continues), Company agrees not to release information from the Phase II Analysis Report or from Company's use of the associated data beyond the named limited group of Company employees without authorization from NIAID (DAIDS). NIAID (DAIDS), in discussion with the ACTIV Trial Oversight Committee, will make the final determination regarding the graduation of the Study Product from Phase II to Phase III. Following unblinding of the data and completion of the primary analysis, Company will be provided with the data.

11.4 In accordance with NIH Grants Policy, data obtained from the Clinical Trial is the property of the Investigator or the Clinical Research Site, as applicable, which produces such data. However, other than Company, its contractors and its designees, no party may review or use the data obtained from the Clinical Trial for purposes of seeking regulatory approval of the Study Product without the written permission of Company.

11.5 Upon completion of the data analysis for the Study Product, NIAID (DAIDS) will authorize the SDMC to transfer to Company a copy of the raw data and data analysis set related to the Study Product and control in a machine-readable format to be determined jointly by the Parties. If Company requires that the data be provided in a customized format(s), Company will pay for all costs associated with the customized data format(s).

11.6 Subject to the right of NIAID (DAIDS) and the Investigators to publish the data from this Clinical Trial as set forth in the Publications and Press Releases Section of this Agreement, Company has the right to utilize the data reports from this Clinical Trial in its possession for all legitimate business or regulatory purposes. NIAID (DAIDS) and/or Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA, the HA(s) and the Securities and Exchange Commission (SEC), for all legitimate public health, regulatory or business purposes. Except for information related to regulatory or safety issues or under emergency circumstances where it is not practicable to do so and to the extent permitted by law, NIAID (DAIDS) will not release information regarding the Clinical Trial to governmental organizations without prior notification to Company.

11.7 NIAID (DAIDS), through its contractor, will be responsible for preparing the final Clinical Study Report in accordance with ICH E3, "Structure and Content of Clinical Study Reports" and will provide a copy of the Clinical Study Report for the Company Study Product to Company.

11.8 Both Parties acknowledge that, should the Clinical Trial results be positive, Company will be responsible for any and all marketing authorization submissions.

12. PUBLICATIONS AND PRESS RELEASES

12.1 Any publications based on the results of the Clinical Trial and originating from NIAID (DAIDS) or the Investigators will conform to the latest version of the ACTG Publication and Disclosure of Study Results Standard Operating Procedure, incorporated herein as Addendum II. Unless requested otherwise by Company, NIAID (DAIDS) will acknowledge Company as the source of the Study Product in any NIAID (DAIDS) publication resulting from the Clinical Trial and will ensure that the Investigators do the same in their publications resulting from the Clinical Trial.

12.2 Recognizing that employees of either Party may play an important role in the design, analysis and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the generally accepted customs pertaining to authorship. NIAID (DAIDS) will ensure that the Investigators include appropriate individuals from both Parties in their publications resulting from the Clinical Trial.

12.3 Each Party will provide, and NIAID (DAIDS) will ensure that the Investigators provide, a copy of any abstract or manuscript to the other Party prior to submission for publication with sufficient time for review and comment, as outlined in the ACTG Publications Standard Operating Procedure [Manuscripts: ten (10) days; Abstracts: five (5) days]. The publication or other disclosure may be delayed for up to thirty (30) additional business days for manuscripts and up to five (5) business days for abstracts, upon written request by either Party as necessary to preserve U.S. or foreign Patent or other intellectual property rights. Each Party agrees that, following the receiving Party's review of the manuscript and/or abstract for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish, present or use any Clinical Trial data. Notwithstanding the timelines described above, the Parties agree that expedient publication of the Clinical Trial results is necessary for the public good and the Parties agree to work in good faith to allow expeditious publication of the Clinical Trial results.

12.4 Each Party will provide, and NIAID (DAIDS) will ensure that the Investigators provide, a copy of any proposed press release to the other Party for review at least five (5) business days in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish the press release.

12.5 Notwithstanding anything to the contrary herein in this Section, NIAID agrees that under no circumstances will it publish in any press release any of the Company's Confidential Information absent Company's prior written consent. Company will make reasonable efforts to supply substitute non-Confidential Information in order to allow the press release to go forward.

13. CONFIDENTIAL INFORMATION

13.1 Either Party may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct the Clinical Trial. The disclosing Party will place a confidentiality notice on all the Confidential Information. The disclosing Party will reduce confidential non-written communications to writing within thirty (30) business days of first disclosure. Each Party receiving Confidential Information agrees that any information so designated will be used by it only for the purposes of the Clinical Trial. Any Party may object to the designation of information as Confidential by the other Party. Any Party that fails to mark tangible Confidential Information as "Confidential" may remedy such failure by providing written notice to the other Party and such remedy shall be effective on the day the notice was received by the receiving Party.

13.2 Unless expressly provided otherwise, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA), 5 U.S.C. § 552, or other applicable laws and/or regulations to disclose the Confidential Information, except that NIAID (DAIDS) and Company may disclose Confidential Information to those of their representatives, agents, officers, attorneys, grantees, contractors, consultants, employees, Affiliates (and Affiliates' directors), directors, advisors and potential Clinical Research Sites (collectively, "Agents") to the degree necessary to conduct the Clinical Trial. The Parties will ensure that their respective Agents maintain the confidentiality of Confidential Information in accordance with the terms of this Agreement.

13.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. Current NIH policy requires that a brief synopsis, the enrollment status and study results for all NIH-funded clinical trials be posted in the ClinicalTrials.gov registry of clinical studies, available through the NIH website. NIAID (DAIDS) shall be responsible for submitting information to ClinicalTrials.gov. Except as expressly provided in this Section 13, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the written consent of the disclosing Party.

13.4 NIAID (DAIDS) acknowledges that the Manufacturing Know-How may be Confidential Information of Company and may be exempted from release under FOIA.

13.5 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given an opportunity to seek a court order to enjoin from disclosure.

13.6 If the receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Section 13.2, becomes legally required to disclose any of the Confidential Information, the receiving Party shall, to the extent practicable, consult with the disclosing Party prior to any disclosure.

13.7 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above, or three (3) years after the expiration or termination date of this Agreement. Either Party may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

14. INTELLECTUAL PROPERTY

14.1 Ownership of any invention made solely or jointly by NIAID (DAIDS), the Clinical Research Sites and Investigators, or other NIAID (DAIDS) contractors or grantees as a consequence of conducting the Clinical Trial and involving the Study Product, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party claims by virtue of this Agreement any right, title, or interest in or to any issued Patents or pending Patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by Company to NIAID (DAIDS) with respect to the Study Product, other than the limited right to use the Study Product for the performance of the Protocol in accordance with the terms of this Agreement.

14.2 **NIAID (DAIDS) Intellectual Property.**

14.2.1 The Government will retain title to any Patent or other intellectual property rights in inventions made by NIAID (DAIDS) employees in the course of the Clinical Trial.

14.2.2 NIAID (DAIDS) agrees to notify Company of any such Invention and is willing to disclose it to Company under an appropriate confidentiality agreement. Company may apply for exclusive license rights to any patentable Invention made by NIAID (DAIDS) employees that might arise during the clinical research and the NIH will consider Company's application for a nonexclusive or exclusive license consistent with 37 C.F.R. Part 404.

14.3 **Company Intellectual Property.** Company will retain title to any Patent, pending patent applications or other intellectual property rights in Inventions made by its employees during the course of the Clinical Trial.

14.4 **Clinical Research Site/Investigator Intellectual Property.** This Agreement does not grant any license or obligation to license any intellectual property, or preclude intellectual property rights, including, but not limited to, Inventions made by ACTG, the Investigators, the Clinical Research Sites or other NIAID (DAIDS) contractors or grantees during the course of the Clinical Trial. Company may enter into a separate agreement with the Clinical Research Sites or Investigators regarding intellectual property rights and confidentiality that do not interfere with the conduct of this Clinical Trial or contradict the terms of this Agreement.

14.5 **Joint NIAID (DAIDS)--Company Intellectual Property.** NIAID (DAIDS) and Company will have joint intellectual property rights in Inventions made jointly by their employees during the course of the Clinical Trial. Company may apply for a non-exclusive or exclusive license to NIAID (DAIDS)'s rights in such Inventions in accordance with 37 CFR 404.

15. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its commercially reasonable efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

16. LIABILITY, INDEMNIFICATION AND INSURANCE

16.1 **Liability.** Activities carried out under this Agreement are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) as implemented under the amended declaration, "Public Readiness and Emergency Preparedness Act Coverage for medical countermeasures against COVID–19," issued on March 17, 2020 (85 Federal Register 15198). The PREP Act provides immunity from liability claims against manufacturers, distributors, program planners and other qualified persons ("Covered Persons") arising from the administration and use of covered countermeasures, as specified in a declaration by the Secretary of HHS ("Secretary") [See section 319F-3 of the Public Health Service Act (42 U.S.C. §247d-6d)]. The exception to this immunity is acts of willful misconduct by the Covered Persons. (i) The Study Product is considered a drug to treat, prevent or mitigate COVID-19, and as such is a covered countermeasure under the Secretary's declaration, and (ii) Company asserts that it is a "covered person" with respect to all "claims for loss" caused by, arising out of, relating to or resulting from the "administration" or the "use" of the Study Product, which is a "covered countermeasure" against COVID-19, as set forth more fully in the PREP Act 42 U.S.C.

§247d-6d(b), and the PREP Act Declaration issued by the Secretary of the Department of the Health and Human Services effective as of February 4, 2020. Informed consent forms used in the Clinical Trial will include a sufficient description of the PREP Act for participants to understand that all Covered Persons have immunity from liability under the PREP Act, and what compensation may be available under the PREP Act Countermeasure Injury Compensation Program [See section 319F-4 of the Public Health Service Act (42 U.S.C. §247d-6e)]. To the extent that PREP Act coverage is not available, each Party shall be liable for any loss, claim, damage or liability that it incurs as a result of its direct activities under this Agreement, except that NIAID (DAIDS), as an agency of the U.S. Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171.

16.2 **Indemnification.** NIAID (DAIDS) is prohibited under the Anti-Deficiency Act, 31 U.S.C. § 1341 from indemnifying Company for any losses incurred as a result of this Clinical Trial. Each Party will be liable for the losses, claims, damages or liabilities that it incurs as a result of its activities under this Agreement. Company's right and obligation to defend NIAID (DAIDS) and Company's control over the defense and settlement of any claim against NIAID (DAIDS) will be subject to the consent of NIAID (DAIDS) and the Department of Justice.

16.3 To the extent that PREP Act coverage is not available, Company will defend, indemnify and hold harmless NIAID (DAIDS)'s grantees and contractors and their respective agents and employees ["Indemnitee(s)"] from any and all liabilities, damages, losses, claims, action, suits and expenses, including attorneys' fees and court costs (collectively "Claims") to the extent caused by the administration or use of the Study Product during the course of the Clinical Trial, provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if each of the following conditions is met:

16.3.1 The Claim was not proximately caused by the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, any written instructions from Company, and this Agreement.

16.3.2 The Claim was not caused by the gross negligence, recklessness or willful misconduct of any Indemnitee, provided that any action properly taken by the Indemnitee in compliance with the Protocol or written instructions from Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if a Claim is jointly caused by the negligence of any Indemnitee and the administration or use of the Study Product, then Company will provide defense and indemnification solely to the extent the Claim was caused by the administration of the Study Product.

16.3.3 Company is promptly notified of the Claim, provided that the failure to give such notice will not abrogate or diminish Company's defense and indemnity obligation if Company has or receives knowledge of the existence of the Claim by any other means and/or if such failure does not prejudice Company's ability to defend the Claim.

16.3.4 Company will have sole control over the defense and settlement of the Claim(s) directed against Company.

16.3.5 Company will have the right to select defense counsel and to direct the defense and settlement of the Claim(s) directed against Company.

16.3.6 Company will provide a diligent defense against and/or settlement of any Claims for which defense and indemnification are provided under this Agreement whether such Claims are rightfully or wrongfully made. Company will have the right to settle such Claims, at Company's sole expense and in Company's sole discretion. Indemnitee(s) will fully cooperate, at Company's expense, with Company and its legal representatives in the investigation and defense of any Claim for which defense and indemnification are provided under this Agreement.

16.3.7 The Indemnitee(s) will at all times have the right to fully participate in the defense of any Claim at their own expense and for their own account. If Company, within a reasonable time after notice, fails to defend any Claim for which defense and indemnification are provided under this Agreement, the Indemnitee(s) will have the right, but not the obligation, to undertake the defense of and to compromise or settle the Claim on behalf, for the account, and at the risk of Company.

16.4 **Participant Injury Attributable to the Clinical Trial**. Company will pay the reasonable cost of medical care required by Clinical Trial participants for illness or injury directly attributable to the Study Product. For purposes of this determination and Company's obligation under this Agreement, "attributable" means that the receipt of the Study Product and the Clinical Trial participant's illness or injury are reasonably related in time, and the illness or injury is more likely explained by the receipt of the Study Product than another cause.

The payment or offer of payment of any amount by Company on behalf of a participant or his or her healthcare insurer or other third party payer under this Section is not an admission of fault or liability by any one or more of (a) the U.S. Government or any agency thereof; (b) the Clinical Research Site or its affiliate organizations, or (c) Company, its employees or agents, and any such payment or offer of payment will not be considered a waiver of any defense or other legal right by any of the foregoing in any legal, administrative or similar proceeding, including the PREP Act, 42 U.S.C. §247d-6d(b) and the PREP Act Declaration issued by the Secretary of the HHS effective as of February 4, 2020. Company reserves the right to seek reimbursement of any medical care costs advanced pursuant to this section 16.3.

16.5 **Insurance.** Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the research related injury and indemnification obligations assumed under this Agreement. Upon request, Company will provide evidence of its insurance or self-insurance to NIAID (DAIDS).

17. DISPUTE RESOLUTION

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the dispute will be referred to the Director of **DAIDS,** NIAID (or his/her designee) and an appropriate authorized representative of Company for resolution. If the Director of DAIDS (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute through good faith negotiations within thirty (30) days, the dispute will be referred to the Director of **NIAID** (or his/her designee) and the authorized representative of Company. If the Director of NIAID (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute, either Party may pursue any and all administrative or judicial remedies that may be available.

18. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the other Party, enter into any contract, warranty or representation as to any matter. Neither Party will be bound by the acts of the other Party.

19. NON-ENDORSEMENT

By entering into this Agreement, NIAID (DAIDS) does not directly or indirectly endorse any product or service provided, or to be provided, by Company. Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However, Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

20. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

21. SURVIVABILITY

The provisions of Sections 2 (Clinical Research Sites and Investigators), 3 (Investigational New Drug Application Sponsorship), 6 (Manufacture, Supply, Distribution and Use of Study Product), 10 (Human Subjects Protection), 11 (Data Collection, Analysis and Management), 12 (Publications and Press Releases), 13 (Confidential Information), 14 (Intellectual Property), 16 (Liability, Indemnification and Insurance), 17 (Dispute Resolution), 18 (Independent Contractors), 19 (Non-Endorsement), 20 (Amendments), this Section 21 (Survivability), and sub-Section 25.4 will survive the expiration or earlier termination of this Agreement.

22. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement. The provisions of this Agreement are severable and, in the event that any provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

23. ASSIGNMENT

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without prior written notification to the other Party. However, Company will have the right to assign this Agreement to an Affiliate without prior written notice to NIAID (DAIDS). The terms and conditions of this Agreement shall be binding on and inure to the benefit of the permitted successors and assigns of the Parties.

24. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

25. TERM AND TERMINATION

25.1 Unless terminated sooner in accordance with this Term and Termination Section, this Agreement will expire upon completion of the Clinical Trial activities and delivery of the Clinical Study Report.

25.2 The Parties may terminate this Agreement at any time by mutual written consent.

25.3 Either Party may unilaterally terminate this Agreement at any time by giving written notice at least thirty (30) days prior to the desired termination date or NIAID (DAIDS) may terminate immediately based on safety considerations.

25.4 The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol, and Company will supply enough Study Product to complete the Clinical Trial. In the event that Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution,

Company must notify NIAID (DAIDS) within at least thirty (30) days of the dissolution.

26. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt), Portable Document Format (PDF) or email followed by conformational hard copies when requested.

For Company:

(b)(6)
(b)(6)
1800 Concord Pike
Wilmington, DE 19850-5437
Phone: (b)(6)
E-mail: (b)(6) @astrazeneca.com

For regulatory matters:

(b)(6)
(b)(6)
One MedImmune Way
Gaithersburg, MD 20878
Phone: (b)(6)
E-mail: (b)(6) @astrazeneca.com

For technical matters:

(b)(6)
(b)(6)
One MedImmune Way
Gaithersburg, MD 20878
Phone: (b)(6)
E-mail: (b)(6) @astrazeneca.com

For NIAID (DAIDS):

Peter S. Kim, M.D.
Director
Therapeutics Research Program
DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9E50
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @nih.gov

For regulatory matters:

Mary Anne Luzar, Ph.D., M.S.
Chief
Regulatory Affairs Branch
DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9B30
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

For clinical matters:

Arzhang Cyrus Javan, M.D., M.P.H., D.T.M.&H.
Medical Officer
DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9E40
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @nih.gov

27. COUNTERPARTS

This Agreement may be executed in one or more counterparts, each of which will be deemed to be an original copy of the Agreement, and all of which, when taken together, will be deemed to constitute one and the same Agreement. Signatures to this Agreement transmitted by fax, by electronic mail in portable document format (PDF), or by any other electronic means intended to preserve the original graphic and pictorial appearance of the Agreement, will have the same effect as physical delivery of the paper document bearing the original signature.

28. LICENSURE

Company agrees that should the Study Product prove to be an effective treatment for COVID-19, Company's general intent is to pursue license of the Study Product in the countries where the Clinical Trial is located.

SIGNATURES BEGIN ON THE NEXT PAGE

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

Peter S. Kim -S Digitally signed by Peter S. Kim -S
Date: 2020.12.15 23:22:51 -05'00'

(Signature) (Date)

Peter S. Kim, M.D.
Director
Therapeutics Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health

(b)(6)

16 December 2020

(Signature) (Date)

(b)(6)
Authorized Signatory
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19803

cc: Principal Investigators, Clinical Research Sites

DAIDS PROTOCOL REGISTRATION MANUAL

Office for Policy in Clinical Research Operations Division of AIDS

EFFECTIVE

DAIDS PROTOCOL REGISTRATION MANUAL

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DAIDS PROTOCOL REGISTRATION MANUAL i

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I. Introduction

The Division of AIDS (DAIDS) Office for Policy in Clinical Research Operations (OPCRO) has established a protocol registration manual that details, in a step-wise manner, the protocol registration process to ensure that all clinical research sites (CRSs) conducting National Institute of Allergy and Infectious Disease (NIAID)DAIDS-supported and/or -sponsored clinical research do so in accordance with DAIDS Clinical Research Policies and Standard Procedures in addition to all applicable regulations for human subjects protection and the use of investigational drugs, biologics and/or devices. Each CRS will complete the protocol registration process for all clinical research supported and/or sponsored by NIAID (DAIDS) that is reviewed by CSRC or PSRC. Submission of an incomplete package by failing to include all required documents for protocol registration at the time of submission to the DAIDS PRO will result in processing delays until all the required documents are received.

The DAIDS Protocol Registration Manual is a reference tool to help CRSs successfully complete the DAIDS protocol registration process. This manual explains the different types of protocol registration submissions as well as a list of the required documents for each type of submission. Critical pointers are provided in the NOTES throughout the DAIDS Protocol Registration Manual. Failure to include any required documents for protocol registration at the time of submission to the DAIDS PRO will result in processing delays until all the required documents are received.

The protocol registration process begins once a protocol has completed the DAIDS protocol development requirements. All protocols must receive final DAIDS approval either after DAIDS Clinical Sciences Review Committee (CSRC) or Prevention Sciences Review Committee (PSRC) and after regulatory review and DAIDS Medical Officer sign-off. For protocols conducted under a DAIDS-held Investigational New Drug (IND) Application, the final DAIDS approved version of the protocol must be submitted to the U.S. Food and Drug Administration (FDA).

The DAIDS protocol registration process verifies that CRSs have received the necessary Institutional Review Board (IRB)/Ethics Committee (EC) and other applicable Regulatory Entity (RE)/Regulatory Authority approvals and have provided to DAIDS all documentation pertaining to investigator qualifications and responsibilities that are required by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the U.S. federal regulations and the National Institutes of Health (NIH). The DAIDS protocol registration process also verifies that site-specific informed consent forms contain the necessary information to comply with ICH, and the U.S. federal regulations. This includes the basic and additional informed consent form elements as required by U.S. federal regulations at 45 CFR 46.116 and 21 CFR 50.25.

II. Summary of Changes

This manual has been reviewed for accuracy and updated to meet 508 compliance guidelines. Several sections have been updated to be consistent with current NIAID (DAIDS) requirements. Key changes to note in this version of the Manual include:

1. DAIDS requirement of Protocol Signature Page (PSP) to document the commitment of the Investigator of Record (IOR) to conduct the trial in compliance with regulations/Laws and ensure compliance with ICH E6 GCP 4.5.1 and 5.6.3.

2. The requirement to submit the Clinical Trial Application (CTA) Form/documentation that identifies the study sponsor.

3. The requirement to submit translation certificate (or translation documentation) confirming a true and accurate translation of documents from local language into English language.

4. Clarification regarding staff that must be listed on the Form FDA 1572 an/or DAIDS IOR Forms in compliance with U.S. regulations and ICH E6 standards.

5. Adjusted the timeline to submit updated DAIDS IOR Forms and Form FDA 1572s from 30 days to 15 days.

6. Formatting changes and hyperlinks added to improve navigation of the manual.

7. Clarified requirements regarding documents required to be submitted to DAIDS from IRBs, ECs, REs, and Regulatory Authorities.

8. Provide guidance on the use of electronic signatures.

9. Change to requirements regarding justifications for non-submission of Regulatory Authority approvals of full version protocol Amendments and Letter of Amendments (LOA).

10. Clarification of Continuing Review requirements based on the October 2018 FDA guidance, 21 CFR 56.109 and 45 CFR 46.109.

This Manual supersedes the version 3.0 dated April 2015.

III. Protocol Registration Required Documents by Submission Type

DAIDS reviews and approves the latest version of each protocol and Sample Informed Consent Form (ICF) before distribution to the CRSs. CRSs are required to submit the initial version and all subsequent versions of a NIAID (DAIDS) -supported and/or -sponsored protocol, including the DAIDS-approved Sample ICF and site-specific ICFs, to their reviewing IRB/EC and other applicable RE/Regulatory Authority(ies) for review and approval.

Prior to implementing the protocol and enrolling participants, a CRS must receive approval from their IRB/EC and other applicable RE/ Regulatory Authorities. In addition, the CRS must successfully complete the DAIDS protocol registration process. When cleared to open to enrollment, a CRS will be notified by the appropriate DAIDS scientific program (e.g., Program/Contracting Officer Representative), Operations Center or Data Management Center when enrollment may begin.

Detailed information on specific requirements for each required document for protocol registration is included in sub-sections A-H of Document Requirements (Concise) of the manual.

A. Submission Requirements by Submission Type

Submission Type	Submission Requirements	Document Requirement	Page
Initial Registration	Form FDA 1572 for IND studies and DAIDS IOR Form for Non-IND studies	Form FDA 1572/DAIDS IOR Form	10
	IOR CV	Curriculum Vitae	11
	IOR Medical License (License equivalent)	Medical License	12
	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submissions Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Documentation of Pediatric risk/benefit category per 45 CFR 46 and 21 CFR 50 (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Clinical Trial Application Form/document	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Regulatory Entity (RE)/Regulatory Authority Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority/Acknowledgement Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All RE/Regulatory Authority Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IBC Approval Letter and applicable correspondence (when applicable)	Institutional Biosafety Committee (IBC)	13
	Protocol Signature Page	Protocol Signature Page (PSP)	14

Submission Type	Submission Requirements	Document Requirement	Page
	Site Specific Informed Consent(s) - all applicable languages. All ICFs required by the protocol are required to be submitted or justification for the omission is required.	Site Specific Informed Consents	15
	Site Specific Informed Assent(s) - all applicable languages	Site Specific Informed Consents	15
	Translation Certificate (if applicable)	Translation requirements	36
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Amendment	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Documentation of Pediatric risk/benefit category per 45 CFR 46 and 21 CFR 50 (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Approval/Acknowledgement Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All RE/Regulatory Authority Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Protocol Signature Page	Protocol Signature Page (PSP)	14
	Site Specific ICF - all applicable languages. All previously approved ICFs must be submitted or justification provided for their omission must be provided. Any new ICFs added within the protocol ICFs must be submitted as an Additional ICF type or justification provided for their omission must be provided.	Site Specific Informed Consents	15

Submission Type	Submission Requirements	Document Requirement	Page
	Site Specific Informed Assent(s) - all applicable languages. All previously approved Assents must be submitted, or justification provided for their omission must be provided. Any new Assents required must be submitted as Additional ICF types or justification provided for their omission must be provided.	Site Specific Informed Consents	15
	Translation Certificate (if applicable)	Translation requirements	36
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Letter of Amendment (LOA)	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submissions Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Documentation of Pediatric risk/benefit category per 45 CFR 46 and 21 CFR 50 (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Approval/Acknowledgement Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Site Specific ICFs - all applicable languages. Any revised ICFs should be submitted as a Site Revised ICF submission along with the LOA. Any new ICFs added within the protocol ICFs must be submitted as an Additional ICF type or justification provided for their omission must be provided.	Site Specific Informed Consents	15

Submission Type	Submission Requirements	Document Requirement	Page
	Site Specific Informed Assent(s) - all applicable languages. Any revised Assent forms should be submitted as a Site Revised ICF submission along with the LOA. Any new Assents required must be submitted as Additional ICF types or justification provided for their omission must be provided.	Site Specific Informed Consents	15
	Protocol Signature Page	Protocol Signature Page (PSP)	14
	Translation Certificate (if applicable)	Translation requirements	36
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Administrative Registration	Form FDA 1572 for IND studies and Form FDA 1572 or IOR Form for Non-IND studies	Form FDA 1572/DAIDS IOR Form	10
	IOR CV	Curriculum Vitae	11
	IOR Medical License (License equivalent)	Medical License	12
	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submissions Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
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	All RE/Regulatory Authority Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IBC Approval Letter and applicable correspondence (when applicable)	Institutional Biosafety Committee (IBC)	13
	Protocol Signature Page	Protocol Signature Page (PSP)	14
	Translation Certificate (if applicable)	Translation requirements	36

Submission Type	Submission Requirements	Document Requirement	Page
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Change of Investigator	Form FDA 1572 for IND studies and Form FDA 1572 or IOR Form for Non-IND studies	Form FDA 1572/DAIDS IOR Form	10
	IOR CV	Curriculum Vitae	11
	IOR Medical License (License equivalent)	Medical License	12
	Protocol Signature Page	Protocol Signature Page (PSP)	14
Continuing Review	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
Site Initiated Revised ICFs	IRB/EC Approval Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	IRB/EC Submission Letters	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	All IRB/EC Correspondence	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority/ Acknowledgement Letters (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Submission Letters (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	RE/Regulatory Authority Approval/Acknowledgement Letters (if applicable)	IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation	12
	Site Specific ICFs - all applicable languages	Site Specific Informed Consents	15
	Site Specific Informed Assent(s) - all applicable languages	Site Specific Informed Consents	15
	Translation Certificate (if applicable)	Translation requirements	36

Submission Type	Submission Requirements	Document Requirement	Page
	Translation Confirmation Documentation (if applicable)	Translation requirements	36
Updated Form FDA 1572 or DAIDS IOR Form	Form FDA 1572 for IND studies and Form FDA 1572 or IOR Form for Non-IND studies	Form FDA 1572/DAIDS IOR Form	10
Deregistration	Request stating that the CRS no longer intends to participate in the protocol(s) and/or A Copy of the IRB/EC closure/termination letter for the protocol if the protocol has been closed with the IRB/EC at the time of deregistration	Deregistration	57
Suspension or Termination of IRB/EC Approval	Documentation from the IRB/EC that identifies the reason for suspension or termination	Suspension or Termination of IRB/EC Approval	31

IV. Document Requirements (Concise)

A. Form FDA 1572/DAIDS IOR Form

Section	General Requirement	Detailed Requirement
Section 1 - Name and Address of Investigator of Record (IOR)	Complete legal name (first and last name) and address of the IOR at the CRS that is responsible for the conduct of the clinical trial. The complete legal name of the IOR and the IOR's complete office address (complete physical location/street address/country)	Section 1 - Name and Address of Investigator of Record (IOR)
Section 2 - Education, Training, and Experience	Requires the IOR to check the appropriate box on how they plan to verify their education, training and experience that qualifies them as an expert in the clinical investigation of the study product (drug or biologic) being tested	Section 2 - Education, Training, and Experience
Section 3 - Name and Address of Location(s) Where the Study Will be conducted	Complete name and address of all locations where the clinical trial will be conducted and where clinical data will be generated or collected. The complete name and physical address of all the locations (medical school, hospital, clinics, additional locations, or research facility)	Section 3 - Name and Address of Location(s) where the Study will be conducted
Section 4 - Name and Address of Clinical Laboratory	Complete name(s) and complete physical address (including country) of ALL clinical laboratories or testing facilities which will be used for the clinical trial to process study related and/or study defined samples that will directly contribute to or support the clinical trial	Section 4 - Name and Address of Clinical Laboratory
Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/ Regulatory Authority(ies)) and Institutional Biosafety Committees (IBCs)	Complete name and address of all IRBs, ECs and other applicable Regulatory Authority(ies) and IBCs which are responsible for the review and approval for the conduct of clinical trials at a CRS	Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/Regulatory Authority(ies) and Institutional Biosafety Committees (IBCs)
Section 6 - Names of Sub-Investigators	Complete legal name (first and last name) of study staff at a CRS responsible for making a "direct and significant contribution to data"	Section 6 - Names of Sub-Investigators
Section 7 - Protocol Name and Protocol Number	DAIDS ES/Network protocol ID number and the complete protocol title	Section 7 - Protocol Name and Protocol Number
Section 8 - Clinical Protocol Information	Leave blank	Section 8 - Clinical Protocol Information
Sections 9 - Commitments	Read and understand	Sections 9, 10 and 11

Section	General Requirement	Detailed Requirement
Section 10 - Date	Handwritten or electronic date is acceptable. If utilizing electronic date, an electronic signature must be utilized, and the electronic date and the date identified in the electronic signature must correspond. See Signature Requirement Guidance regarding electronic signature requirements.	Sections 9, 10 and 11
Section 11 - Signature of Investigator	Handwritten or electronic signature is acceptable. If utilizing electronic signature, an electronic date must be utilized and the electronic date and the date identified in the electronic signature must correspond See Signature Requirement Guidance regarding electronic signature requirements.	Sections 9, 10 and 11

B. Curriculum Vitae

	General Requirement	Detailed Requirement
Curriculum Vitae (CV)	Submitted (or on file and less than two years old)	Curriculum Vitae (CV)
	Name on the CV matches IOR identified on current Form FDA 1572 or DAIDS IOR Form	
	Complete (all pages submitted, and the document is legible)	
	Dated: Handwritten or electronic date is acceptable. If utilizing electronic date, an electronic signature must be utilized, and the electronic date and the date identified in the electronic signature must correspond. See Signature Requirement Guidance regarding electronic signature requirements.	
	Signed: Handwritten or electronic signature is acceptable. If utilizing electronic signature, an electronic date must be utilized and the electronic date and the date identified in the electronic signature must correspond See Signature Requirement Guidance regarding electronic signature requirements.	

C. Medical License

	Review Requirement	Detailed Requirements
Medical License (ML)	Name on the ML or equivalent document matches IOR identified on current Form FDA 1572 or IOR Form	Curriculum Vitae (CV) and Medical License
	The ML or equivalent document is current (not expired). Note that if the ML does not designate an expiration date, it can be accepted.	

D. IRB/EC/Regulatory Entity(ies)/Regulatory Authority(ies) documentation

	Review Requirement	Detailed Requirements
IRB/EC/RE/Regulatory Authority(ies)	Complete protocol title or short title for the current DAIDS approved version of the protocol.	IRB/EC Approvals
	DAIDS-ES and/or Network Protocol ID	
	DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS and/or the final version date of the protocol document	Regulatory Entity (RE)/Regulatory Authority Approvals
	Final approval letter (conditional approvals not accepted)	
	Pediatric Risk Assessment included in the IRB approval Letter, if applicable	Documentation of Pediatric Risk/Benefit Category
	For LOAs and full version protocol amendments - The date that the amended protocol documents were submitted to the reviewing IRB/EC must be identifiable or provided on the IRB/EC approval letter or on the memo/CRS note, and the date must predate the final IRB/EC approval	Amendment Registrations
		Letter of Amendment (LOA) Registration
	Approval letters from all applicable IRB/EC/ RE/Regulatory Authority(ies) as listed on the Form FDA 1572 or DAIDS IOR Form or justification for their omission	Amendment Registrations
		Letter of Amendment (LOA) Registration

E. Institutional Biosafety Committee (IBC)

	Review Requirement	Detailed Requirements
Institutional Biosafety Committee (IBC)	Complete protocol title or short title for the current DAIDS approved version of the protocol	Institutional Biosafety Committee (IBC) Approval
	DAIDS-ES and/or Network Protocol ID	
	DAIDS Protocol Version Number from the final version of the protocol as approved by DAIDS and/or the final version date of the protocol document	
	Final approval letter (conditional approvals not accepted)	

F. Protocol Signature Page (PSP)

	Review Requirement	Detailed Requirements
Protocol Signature Page (PSP)	Submitted for Initial, Amendment or LOA and Change of IOR submissions Contains the following statement verbatim, "I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies."	Protocol Signature Page (PSP)
	Signed by the IOR (s) that is listed on item #1 on the site's current Form FDA 1572/DAIDS IOR Form on file at DAIDS. Handwritten or electronic signature is acceptable. If utilizing electronic signature, an electronic date must be utilized, and the electronic date and the date identified in the electronic signature must correspond. See Signature Requirement Guidance regarding electronic signature requirements.	
	Dated: Handwritten or electronic date is acceptable. If utilizing electronic date, an electronic signature must be utilized, and the electronic date and the date identified in the electronic signature must correspond. See Signature Requirement Guidance regarding electronic signature requirements.	
	Lists the complete DAIDS Protocol Title	
	Lists the DAIDS Protocol Number	
	Lists the correct DAIDS Protocol Version (include the protocol and LOA version when applicable)	
	Lists the correct DAIDS Protocol Version Date	

G. Site Specific Informed Consents

	Review Requirement	Detailed Requirements
Site Specific Informed Consent/ Assent Forms	Lists the complete DAIDS Protocol Title	Site-Specific Informed Consent Forms (ICFs)
	Lists the DAIDS Protocol Number	
	Lists the correct DAIDS Protocol Version	
	All ICFs included in the DAIDS approved protocol are submitted or justification for their omission is provided	
	All ICFs are submitted in all applicable languages or justification for their omission is provided	
	All ICFs should meet all requirements as specified in CFR 46.116, 21 CFR 50.25 DAIDS Policy DWD-POL-CL-02.00 and local laws and regulations	
	Full version protocol Amendments only - All ICFs Types previously registered as part of initial registration are submitted or justification for their omission is provided	

H. Clinical Trial Applications Form/Document

	Review Requirement	Detailed Requirements
Clinical Trial Application Form/Document	Lists the complete DAIDS Protocol Title	Clinical Trial Applications (CTA) for In-country Regulatory Entity (RE)/Regulatory Authority(ies)
	Lists the DAIDS Protocol Number	
	Lists the correct DAIDS Protocol Version	
	Lists the correct DAIDS Protocol Version dated	
	Documentation to confirm that the correct sponsor is identified	
	Complete (all pages) and legible	

V. Protocol Registration Required Documents (Detailed)

A. Form FDA 1572/DAIDS IOR Form

REQUIRED FOR:

- INITIAL REGISTRATION
- WHEN THERE IS ANY MAJOR CHANGE TO THE INFORMATION ON THE CURRENT FORM FDA 1572/DAIDS IOR FORM.

Form FDA 1572 must be submitted for studies being conducted under an IND application. The DAIDS IOR Form or Form FDA 1572 can be submitted for an initial registration for studies not conducted under an IND application.

A signed Form FDA 1572/DAIDS IOR Form is required for each investigator that participates in any clinical trial (drug or biologic). By signing the Form FDA 1572/DAIDS IOR Form, the Investigator of Record (IOR) affirms that he/she will conduct the clinical trial according to the research protocol and all applicable U.S. federal regulations and the ICH E6 GCP guidelines. By signing the Form FDA 1572/DAIDS IOR Form, investigators at non-U.S. sites affirm to DAIDS their commitment to comply with local laws and regulations throughout the course of the clinical trial.

All CRSs participating in a NIAID (DAIDS)-supported and/or -sponsored clinical trials conducted under an IND must submit a copy of the signed and dated Form FDA 1572 to the DAIDS PRO as part of the protocol registration submission for review and for submission to the U.S. FDA.

NOTE: *CRSs are required to retain the original signed Form FDA 1572/DAIDS IOR Form in their regulatory files at the site. Original Forms should not be sent to the DAIDS PRO.*

CRSs requiring more space than what is provided on the Form FDA 1572/DAIDS IOR Form can use a supplemental page. The supplemental page provides additional space to document: additional research locations and addresses; laboratory facilities and addresses; and the names of additional sub-investigators. The supplemental page should identify the CRS and protocol number. If used, a copy of the supplemental page must also be sent to the DAIDS PRO as part of the protocol registration submission.

A CRS must update and submit within 15 calendar days a revised copy of the Form FDA 1572/DAIDS IOR Form when there is ANY major change to the information on the current Form FDA1572/DAIDS IOR Form submitted to the DAIDS PRO. Any correction or revision requires the IOR to sign and date the newly revised form. CRSs must submit BOTH pages of the revised Form FDA 1572/DAIDS IOR Form to the DAIDS PRO even if the changes only affect one page of the form. An updated Form FDA 1572/DAIDS IOR Form that has the same date as the original or previous version will not be accepted.

NOTE: *Examples of major changes to the Form FDA 1572/DAIDS IOR Form include but are not limited to:*

- *Change in IOR*
- *Change in Sub-IOR*
- *Addition of a new or additional DAIDS approved location where the research will be conducted*
- *Addition of a laboratory*
- *Addition or change in an IRB/EC/ RE/Regulatory Authority(ies) that is responsible for review and approval of the clinical research protocol*

The most current version of the Form FDA 1572/DAIDS IOR Form is available for download on the DAIDS RSC Website under the "Protocol Registration" section or from the U.S. FDA website.

B. How to complete the Form FDA 1572/DAIDS IOR Form

Below is detailed information to assist a CRS when completing these Forms.

1. Section 1 - Name and Address of Investigator of Record (IOR)

This section must contain the complete legal name (first and last name) and complete office address (complete physical location/street address) address of the IOR at the CRS that is responsible for the conduct of the clinical trial. Non-U.S. CRSs should include the complete physical address, including
the country.

If a CRS has more than one IOR sharing responsibilities for a clinical trial, the CRS has the following options:

- The CRS can submit a separate Form FDA 1572/DAIDS IOR Form for each IOR that is responsible for the study at that CRS(s) and other DAIDS approved location(s). The CRS must provide documentation explaining that the investigators listed on the two Form FDA 1572s/DAIDS IOR Forms are sharing responsibilities for the conduct of the study at the CRS and DAIDS approved additional location(s).
- The CRS can submit one Form FDA 1572/DAIDS IOR Form that lists both investigators in Section 1 of the Form FDA 1572. This indicates that both

investigators are sharing equal responsibilities for the conduct of the study at the CRS(s) and other DAIDS approved location(s). Each investigator must date sections 10 and sign Section 11 of the Form FDA 1572/DAIDS IOR Form.
The CRS must provide documentation stating that the two investigators listed on the Form FDA 1572 are sharing responsibilities for the conduct of the study at the CRS(s) and other DAIDS approved location(s).

NOTE: *Requirements for the documentation regarding shared responsibilities can be fulfilled in one of the following ways:*

- *Provide a written document that specifies how responsibilities will be shared and the role of each IOR at their respective location(s).*

- *Provide a copy of the study specific Delegation of Duties/Delegation of Responsibility log that indicates how responsibilities will be shared and the roles of each IOR at their respective location(s).*

- *Provide a statement in item 1 of the Form FDA 1572/DAIDS IOR Form that specifies that the two IORs are Co-Investigators and how responsibilities will be shared and the role of each IOR at their respective location(s).*

2. Section 2 - Education, Training, and Experience

This section requires the IOR to check the appropriate box on how they plan to document their education, training and experience that qualifies them as an expert in the clinical investigation of the study product (drug or biologic) being tested. The box marked "Curriculum Vitae" should be checked and a copy of the IOR's CV must be included in the registration packet that is submitted to the DAIDS PRO. DAIDS does not require the submission of CVs for sub-investigators. However, sites should keep a copy of all sub-investigator CVs in the regulatory files at the site. DAIDS requires that all CVs be submitted in English and must be signed and dated.

3. Section 3 - Name and Address of Location(s) where the Study will be conducted

This section must list the complete name and physical address of all locations (medical school, hospital, clinics, satellite sites, or research facility) where the clinical trial will be conducted and where clinical data will be generated or collected. This includes facilities where participants will be seen and study procedures performed. Non-U.S. CRSs should include the country in addition to the complete physical address.

If a CRS utilizes a DAIDS-approved pharmacy, it is not necessary to list the pharmacy on the Form FDA 1572/DAIDS IOR Form. If a CRS out-sources the pharmacy responsibilities

for a clinical trial the CRS must list the name and complete physical address of the contracted pharmacy in Section 3.

If an IOR is conducting the same research protocol at more than one CRS overseen by the same IRB/EC, then it is acceptable to submit one Form FDA 1572/DAIDS IOR Form which lists all locations where the clinical trial will be conducted. If more than one CRS is included in Item 3, include the DAIDS site ID (if available) for each CRS.

4. Section 4 - Name and Address of Clinical Laboratory

This section must list the complete name(s) and complete physical address of ALL clinical laboratories or testing facilities which will be used for the clinical trial to process study related and/or study defined samples that will directly contribute to or support the clinical trial (e.g., diagnostic labs performing blood work, imaging centers, cardiology labs, non-local labs). This may include analytical labs that provide pharmacokinetic analysis, and laboratories supplying efficacy data. The official name of the laboratory (e.g., Department of Pathology) should be included. If multiple CRSs and/or locations are listed on the Form FDA 1572/DAIDS IOR Form, the corresponding clinical laboratories must be listed for each CRS and/or location.

Exceptions for not including ALL clinical laboratories or testing facilities include:

- If a primary laboratory is sending samples to a satellite or other contract labs for additional testing, or
- If a laboratory is being used only to store study samples.

The additional labs do not need to be listed as long as the primary laboratory can trace, through written records, the shipment of samples to the additional labs where the tests were performed.

5. Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/Regulatory Authority(ies) and Institutional Biosafety Committees (IBCs)

This section must list the complete name and address of all IRBs, ECs REs, IBCs and all other Approving Entities including all National Regulatory Authorities which are responsible for the review and approval of clinical trials at a CRS prior to the CRS's initiation of the protocol and during the implementation of the study (if applicable).

NOTE: *In addition to U.S. FDA requirements, DAIDS requires that all sites participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials list all authorities that must review /approve/acknowledge the clinical trial prior to implementation at a CRS.*

These regulatory entities may include any authorities that regulate, provide permits and/or provide authorization before commencing any clinical trial at a CRS.

The official name (refer to the title provided on the IRB/EC and all other RE/Regulatory Authority(ies) approval letter(s)) and complete physical address of the IRBs/ECs and other REs/Regulatory Authority(ies) which reviewed the protocol should be included in Section 5. IRBs/ECs reviewing and approving the clinical trial do not have to be at the same location as the research being conducted.

NOTE: *The DAIDS PRO must receive an approval letter for each entity listed in Section 5 of the Form FDA 1572/DAIDS IOR Form. The RE/* Regulatory Authority *should not be removed/omitted from FORM FDA 1572/DAIDS IOR Form if they are not responsible for/or do not require the review and approval of full version protocol amendments, LOAs or changes to the CRS's site-specific ICF(s). The CRS Leader or IOR must document in writing to the DAIDS PRO and must also provide documentation (letter from the entity or SOP/guidance/regulation/procedure document of the entity) that shows that the entity doesn't review/approve full version protocol amendments/LOAs/Site specific ICs, when submitting registration materials.*

6. Section 6 - Names of Sub-Investigators

This section must list the complete legal name (first and last name) of all study staff at a CRS that are responsible for making a "direct and significant contribution to the data". A direct and significant contribution includes any persons directly responsible for the treatment or evaluation of research participants. This includes site personnel who have more than minimal involvement with the conduct of the research (performing study evaluations or procedures, conducting Informed Consent or providing intervention) or more than minimal study conduct-related contact with study participants or confidential study data, records, or specimens. A study specific Delegation of Duties/Delegation of Responsibilities log must be maintained at the site and should include all persons identified as providing a direct and significant contribution to the data.

Hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care and who do not make a direct and significant contribution to the data do not need to be listed. It is not necessary to include in Section 6 a person with only an occasional role in the conduct of the research (i.e., an on-call physician who temporarily dealt with a possible adverse event or a temporary substitute for any research staff). If a number of residents on rotation will participate in the clinical trial, a general statement regarding their planned participation may be included in Section 6.

The decision about whether to list a pharmacist or research coordinator on the Form FDA 1572/DAIDS IOR Form is the responsibility of the IOR at the CRS and should be based on the contribution that the individual makes to the study.

For example, a research pharmacist may prepare test articles and maintain drug accountability for many clinical trials that are ongoing concurrently at an institution. Because the pharmacist is not making a direct and significant contribution to the data for a particular study, it would not be necessary to list the pharmacist as a sub- investigator in Section 6, but he/she should be listed in the investigator's study records.

CRSs are required to list, at a minimum, a qualified sub-investigator (who will be responsible for fulfilling the requirements of the IOR should the IOR not be able to meet his/her requirement for any given reason). The complete legal name(s) of the sub-investigators who will assist the IOR in the conduct of the protocol should be listed in Section 6.

The IOR is responsible for determining the sub-investigators to be included on the Form FDA 1572/DAIDS IOR Form. Individuals who will sign study medication prescriptions and physicians who submit SAE/EAEs to DAIDS must be listed on the Form FDA 1572/DAIDS IOR Form. The IOR must designate a physician as a sub-investigator who will be responsible to serve as the IOR's backup.

NOTE: *Any physician who is responsible for the review and submission of SAE/EAEs to DAIDS must be listed in Section 6 of the Form FDA 1572/DAIDS IOR Form. Safety reports cannot be submitted by a physician who is not listed in Section 6 of the Form FDA 1572/DAIDS IOR Form.*

NOTE: *CRSs must list the CRS Leader as a Sub-investigator in Section 6 on all Form FDA 1572s /DAIDS IOR Forms if the IOR for the protocol, listed in Section 1, is not the CRS Leader. If the CRS Leader is the same person listed in Section 1 on the Form FDA 1572/DAIDS IOR Form, then the CRS Leader does NOT need to be listed again as a sub-investigator.*

NOTE: *Personnel at facilities where the study uses certain tests (e.g. cardiologist reading ECG or personnel at ECG facilities) do not have to be listed if they are not considered to be engaged in research activities. Per B1 of* OHRP's guidance document on engagement*; not all personnel are considered engaged in research activities unless they have other activities, such as administering study interventions being tested or evaluated or being a collaborator on the publication.*

7. Section 7 - Protocol Name and Protocol Number

The DAIDS ES/Network protocol ID number and the complete protocol title must be included in Section 7. CRSs should not include the DAIDS protocol version number, and/or protocol date in Section 7.

NOTE: *Short titles cannot be accepted and will result in the CRS having to submit a revised Form FDA 1572/ DAIDS IOR Form which will delay protocol registration.*

8. Section 8 - Clinical Protocol Information

NOTE: *The DAIDS IOR Form does not include a Clinical Protocol Information Section*

As the IND sponsor, DAIDS submits the protocol and all relevant information to the FDA on behalf of the investigator. This section should be left blank for both boxes. If DAIDS is not the IND sponsor for a trial, the IND sponsor is responsible for submitting the protocol and all relevant information including the Form FDA 1572 to the FDA and can determine the appropriate information for this section.

9. Sections 9, 10 and 11

NOTE: *These sections are numbered 8, 9, and 10 on the DAIDS IOR Form.*

The IOR must read Section 9, date Section 10 and sign Section 11. The complete legal handwritten or electronic signature of the IOR should be included in Section 11 and should correspond with the name in Section 1 of the Form FDA 1572/DAIDS IOR Form.

NOTE: *If more than one IOR is listed in Section 1 of the Form FDA 1572/ DAIDS IOR Form, both IOR's must sign and date this section.*

NOTE: *Electronic Signature are permissible using the Adobe Acrobat Self-Sign plug-in to insert your signature on fillable FDA forms. Security certificates associated with your digital signatures should be maintained at the site in compliance with 21 CFR 11.1(a). See Signature Requirement Guidance for additional information regarding electronic signatures. If utilizing electronic signatures, the date listed in the date field should be the same date identified on the electronic signature. If signed using hand written signature, the date must also be handwritten.*

NOTE: *If a CRS updates their Form FDA 1572/DAIDS IOR Form, the IOR(s) is responsible for signing and dating the new document even if the change(s) only affect page 1.*

NOTE: *An updated Form FDA 1572/ DAIDS IOR Form that is dated the same as the original or previous version will not be accepted.*

C. Financial Disclosure (FD) by Clinical Investigators

Effective July 1, 2014, any investigator (including sub-investigators) listed on the Form FDA 1572 must complete a financial disclosure (FD) form/statement for all DAIDS sponsored and/or supported studies where DAIDS holds the IND.

Per the regulatory requirements of 21 CFR 54, a person listed as an investigator or sub-investigator on the Form FDA 1572 must complete and submit financial disclosure information for all DAIDS sponsored and/or supported studies where DAIDS holds the IND. Each clinical trial Leadership and Operations Center has developed a generic financial disclosure form/statement for all network studies that are conducted under DAIDS held IND. These forms should be used unless DAIDS or the protocol team provides sites with a different FD Form/statement.

For all Non-Network studies that are conducted under a DAIDS held IND, DAIDS has developed a financial disclosure form/statement and this form is available on the DAIDS RSC website Financial Disclosure Form for Non-Network under Clinical Research Sites.

All original, completed and signed DAIDS approved network financial disclosure Forms/statements or the drug company-specific financial disclosure forms/statements must be filed and retained in a CRS's regulatory binder along with the original and/or updated, signed Form FDA 1572 for that study. These forms need not be submitted to DAIDS or the Network Operations Centers unless requested. For Non-DAIDS held INDs, investigators should follow the IND sponsor's instructions for the collection of financial disclosure form/statement (which may be a company or institution).

If FD forms/statements are required for a regulatory submission, CRS Leaders are responsible for making sure that a financial disclosure form is completed and submitted to their appropriate Network Operations Center per affiliated network requirements for each individual listed in Sections 1 and 6 of the Form FDA 1572.

This process is not required for Non-IND/IDE studies. Refer to the Protocol Registration Frequently Asked Questions on the DAIDS RSC website for additional information on the completion, implementation and collection of FD forms/statements.

D. Curriculum Vitae (CV) and Medical License (ML)

REQUIRED FOR:

- INITIAL REGISTRATION
- WHEN THERE IS ANY MAKOR CHANGE TO THE CURRENT CV ON FILE WITH THE DAIDS PRO.

OR

- UPDATED EVERY TWO YEARS

The IOR overseeing DAIDS-supported and/or sponsored clinical research must provide evidence of qualifications (experience, training and education) to assume responsibility for the conduct of a clinical trial. All CVs must provide sufficient documentation for DAIDS to verify the IOR's qualification to conduct a clinical trial.

IORs must sign and date their CV prior to submission to the DAIDS PRO. All IORs are required to submit an updated, newly signed and dated CV when there is ANY major change to the current CV on file with the DAIDS PRO or at a minimum of every 2 years.

If the IOR is a physician, a copy of the IOR's current medical license documentation or equivalent (i.e., documentation of good standing in the country where they are practicing) must be submitted with all CVs.

NOTE: *Examples of major changes to the IOR CV include but are not limited to:*

- *Change in contact information*
- *Change in education, Change in experience, New trainings*
- *New publications*

U.S. federal regulations require that the IOR's CV be submitted to the U.S. FDA for all studies being conducted under an IND. DAIDS, as the IND sponsor, submits the IOR CV to the U.S. FDA. Sub-investigators are not required to submit CVs to the DAIDS PRO. However, sites should keep a copy of all sub- investigator CVs in the regulatory files at the site.

DAIDS accepts a NIH Bio-Sketch formatted CV that includes education/training, current employment, past relevant employment, licensures/memberships, and any relevant publications.

The NIH Bio-Sketch formatted CV template is available at NIH Grant Application Guide.

NOTE: *Electronic Signature are permissible using the Adobe Acrobat Self-Sign plug-in to insert your signature on fillable FDA forms. Security certificates associated with your digital signatures should be maintained at the site in compliance with 21 CFR 11.1 (See Signature Requirement Guidance for additional information regarding electronic signatures.*

NOTE: *If handwritten signatures are used, the date must also be handwritten.*

E. Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals

REQUIRED FOR:

- ALL INITIAL, AMENDMENT and LOA REGISTRATIONS, ADMINSTRATIVE REGISTRATIONS
- CONTINUING/ ANNUAL REVIEW SUBMISSIONS
- SITE INITIATED REVISIONS TO SITE- SPECIFIC ICFs and SUBMISSION OF REVISED SITE ICF(s) IN RESPONSE TO A DISAPPROVAL NOTIFICATION.

1. IRB/EC Approvals

CRSs are required to submit to their IRB/EC, the initial version and all subsequent full version amendment and LOA versions of NIAID (DAIDS)-supported and/or sponsored clinical trials and observational studies for review and approval, including the DAIDS-approved sample ICF and site- specific ICFs to the DAIDS PRO. The site's submission to the IRB/EC should include DAIDS approved sample protocol and Site ICF, all site specific ICFs, and any material/information that the site plans to provide to participants. CRSs must submit to the DAIDS PRO a copy of ALL documentation to and from the IRB/EC along with a copy of all the final approval letter(s). Original documents should be kept in the regulatory files at the CRS. The IRB/EC approval letter(s) for all initial, full version protocol amendment, and LOA registrations must be a final approval not noting any required modifications or stipulations.

NOTE: *Documentation to and from IRB/EC includes but is not limited to:*

- *the submission letter from the site to the IRB/EC*
- *the letter(s) from the IRB/EC documenting queries and changes required to the site-specific ICFs*
- *site response to the queries*
- *final approval letter(s)*

All IRB/EC approval letter(s) must be able to be linked to the DAIDS-approved version of the protocol. If an IRB/EC approval letter(s) does not include the DAIDS required identifying information in their approval letters, CRSs can submit a memo with their IRB/EC submission that includes: identifying information corresponding to the protocol, lists all the documents submitted for IRB/EC review, as well as the date of submission to the IRB/EC. The required identifying information are:

- Complete Protocol Title as listed on the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both in the DAIDS SAMPLE ICF.

- DAIDS ES and/or Network Protocol ID Number.

- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS and/or the final version date of the protocol document approved by DAIDS.

The CRS's memo/submission letter can be used to document that the IRB/EC/RE/Regulatory Authority received the correct version of the protocol and may be included with the IRB/EC/RE/Regulatory Authority approval letters that are submitted to the DAIDS PRO.

NOTE: *The CRS's memo to the IRB/EC/RE/Regulatory Authority requesting review must pre-date the date on the final IRB/EC/RE/Regulatory Authority approval letter(s).*

NOTE: *Sites are strongly advised to document the date the CRS receives each final IRB/EC/RE/Regulatory Authority approval letter to ensure compliance with the DAIDS protocol registration policy regarding submission of amendment and LOA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final IRB/EC/RE approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.*

NOTE: *If the reviewing IRB transferred the responsibility to another IRB, a site needs to provide documentation of the delegation of authority to the other IRB to the DAIDS PRO*

NOTE: *If any of the IRB/EC/RE/Regulatory Authority approval letter(s) or CRS's memo do not contain enough information to be linked to the most current DAIDS- approved version of the protocol, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

2. Regulatory Entity (RE)/Regulatory Authority Approvals

When other approvals are required in addition to the reviewing IRB/EC at a CRS prior to implementation of a protocol at a CRS, copies of those approval letters and any other appropriate correspondence (as noted in Section 1 above) must be submitted to the DAIDS PRO with registration materials.

NOTE: *If a given RE/Regulatory Authority requires review/approval of initial versions of protocols but does not review and approve full version amendments and LOAs, the CRS Leader or IOR should provide letter/documentation from the Regulatory Authority or by submission of the applicable regulation that defines the specific requirement when submitting registration materials. The CRS Leader or IOR must document in writing to the DAIDS PRO and also provide documentation (letter from the entity or SOP/guidance/regulation/procedure document of the entity) that shows that the entity doesn't review/approve full version protocol amendments/LOAs/Site specific ICs, when submitting registration materials*

NOTE: *In addition to U.S. FDA requirements, DAIDS requires that all sites participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials list all authorities that must review/approve/acknowledge the clinical trial prior to implementation at a CRS. These regulatory entities may include any authorities that regulate, provide permits and/or provide authorization before commencing any clinical trial at a CRS. For information on completing the Form FDA 1572 and/or DAIDS IOR Form, refer to Section V, Sub Sections A and B - "Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)/Regulatory Authority(ies) and Institutional Biosafety Committees (IBCs)"*

3. Clinical Trial Applications (CTA) for In-country Regulatory Entity (RE)/Regulatory Authority(ies)

DAIDS requires the submission of Clinical Trials Applications (CTAs) to DAIDS to ensure compliance with ICH E6. DAIDS requires that a copy of the CTA submitted to the competent National Regulatory Authority(ies) be submitted to the DAIDS RSC to verify the accuracy of the application/submission prior to sites being allowed to complete the initial protocol registration process for a protocol. Refer to the Clinical Trial Application Submission Guidance on how to submit CTA documents to the DAIDS RSC.

Per the DAIDS Policy for Protocol Registration (DWD-POL-RA-011), the in-country Clinical Trial Application Form/Document submitted to National Regulatory Authorities must be submitted to the DAIDS RSC prior to a CRS's being able to participate in the trial. The Clinical Trial Application Form/Document is required for National Regulatory Authorities identified on the Form FDA 1572 or DAIDS IOR Form.

Attachments included with the applications are not required unless required to identify the sponsor and applicable protocol information. See specific document requirements and follow submission instructions as stated in the Clinical Trial Application Submission Guidance.

4. Documentation of Pediatric Risk/Benefit Category

Per the DAIDS Policy for Enrolling Children (including Adolescents) in NIAID (DAIDS)-supported and/or sponsored Human Subject Clinical Research, for research studies including children or adolescents, DAIDS requires documentation of the IRB/EC designation of the pediatric risk/benefit category per the U. S. Federal regulations, 45 CFR 46, 404-407 and 21 CFR 50.51-54 and IRB /EC approval for involvement of children based on the determination specified by that category. This requirement applies to the initial and continuing/annual reviews of research protocols and to any subsequent reviews of full version protocol amendments and LOAs involving potential study risks or benefits. The documentation may be in the IRB/EC approval letter(s) or in other official correspondence from the IRB/EC to the site Investigator.

NOTE: *Failure to submit documentation of the IRB/EC designation of the pediatric risk/benefit category or documentation that the CRS will not enroll children or adolescents at the time of registration submission to the DAIDS PRO will result in delays in protocol registration.*

F. Institutional Biosafety Committee (IBC) Approval

REQUIRED FOR ALL INITIAL REGISTRATIONS FOR RESEARCH THAT INVOLVES RECOMBINANT DNA.

Research supported by NIH funding that involves recombinant DNA is subject to special regulatory oversight by an IBC. In addition, clinical trials testing products containing recombinant DNA must be submitted to the NIH Office for Biotechnology Activities (OBA) for review by the NIH Recombinant DNA Advisory Committee (RAC). Detailed information regarding the requirements for NIAID (DAIDS) -sponsored and/or -supported research involving recombinant DNA is available on the DAIDS RSC website under the “Protocol Registration” section.

Once IBC approval is received, a copy of the final approval letter and any other appropriate correspondence (as noted in Section 1 above) must be submitted to the DAIDS PRO with the initial registration submission. Failure to submit documentation of IBC approval at the time of initial registration submission to the DAIDS PRO will result in delays in protocol registration.

If an IBC must review and approve all full version protocol amendments and LOAs prior to the implementation at a CRS, documentation of the IBC approval should be submitted to the DAIDS PRO at the time of amendment or LOA registration.

All IBC approval letter(s) must be able to be linked to the current DAIDS- approved version of the protocol at the time of initial protocol registration. Since not all IBCs include the DAIDS-required identifying information in their approval letters, a CRS can submit a memo with their IBC submission which lists identifying information corresponding to the protocol, all the documents submitted for review as well as the date of submission to the IBC. The required identifying information are:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS sample informed consent forms.

- DAIDS ES and/or Network Protocol ID Number.

- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS AND/OR the final version date of the protocol document approved by DAIDS.

The CRS's memo can be used to document that the IBC received the correct version of the protocol and may be included with the IBC approval letter that is submitted to DAIDS PRO.

NOTE: *The CRS's memo to the IBC requesting review must pre-date the date on the final IRB/EC approval letter(s).*

NOTE: *If the IBC approval letter or CRS's memo does not contain enough information to be linked to the most current DAIDS-approved version of the protocol, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

G. Protocol Signature Page (PSP)

REQUIRED FOR ALL INITIAL, AMENDMENT, LOA, AND CHANGE OF IOR SUBMISSIONS

DAIDS has implemented a new regulatory requirement effective May 07, 2017 a Protocol Signature Page (PSP) to document the commitment of the IOR to conduct the trial in compliance with the protocol as agreed to by the sponsor and in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

NOTE: *DAIDS does not require submission of the PSP to an IRB/IEC or regulatory authority, unless required by the IRB/EC/RE.*

The following language must be included in all PSPs:

"I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies."

A site should not alter the above template language but may add required language (e.g., institutional requirement) for the IORs commitment to conduct the trial in accordance with all applicable regulations.

All PSPs must be able to be linked to the current DAIDS- approved version of the protocol at the time of protocol registration. The required identifying information are:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS sample.
- DAIDS ES and/or Network Protocol ID Number.
- DAIDS Protocol Version Number (including LOA version when applicable) for the version being registered.
- DAIDS Protocol Version Date for the version being registered.

All PSPs must be signed by the DAIDS approved IOR listed on the Form FDA 1572/DAIDS IOR Form. The PSP is protocol-specific and must be signed by the IOR at each participating site. This responsibility may not be delegated. If there are more than one IOR, a PSP is required for each IOR or a Single PSP can be submitted that is independently signed and dated by each IOR. If there is changes of IOR, an updated PSP is required as part of the Change of IOR submission. All original PSPs must be maintained in the regulatory binder at the site.

NOTE: *Failure to include s signed PSP at the time of submission to the DAIDS PRO will result in processing delays until the required document is received.*

NOTE: *Electronic Signature are permissible using 21 CFR 11.1compliant signatures. Security certificates associated with your digital signatures should be maintained at the site in compliance with 21 CFR 11.1(a). If utilizing electronic signatures, the date listed in the date filed should be the same date identified on the electronic signature. For additional information regarding electronic signatures, please see the Signature Requirement Guidance.*

NOTE: *If handwritten signatures are used, the date must also be handwritten.*

H. Suspension or Termination of IRB/EC Approval

Per U.S. federal regulations, 45 CFR 46.113 the IRB/EC has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's/EC's requirements or that has been associated with unexpected serious harms to participants. The regulations mandate that when the reviewing IRB/EC suspends or terminates its approval of research, this information be reported to, among others, the investigator and sponsor.

Per the DAIDS Critical Events Manual, for any studies that are protocol registered through the DAIDS PRO, the CRS must submit documentation of the suspension or termination of IRB/EC approval to DAIDS as soon as possible, but not later than 3 reporting days through the DPRS. If a study is not registered through the DAIDS PRO, the CRS must notify the appropriate DAIDS Program Officer (PO) or Contracting Officer Representative (COR) of the IRB/EC actions to suspend or terminate IRB/EC approval.

I. Site-Specific Informed Consent Forms (ICFs)

REQUIRED FOR:

- ALL INITIAL, FULL VERSION PROTOCOL AMENDMENT and LOA REGISTRATIONS
- CONTINUING /ANNUAL REVIEW SUBMISSIONS
- SITE-INITIATED REVISIONS TO SITE-SPECIFIC ICFs, and IF THERE WAS A CHANGE TO THE SITE-SPECIFIC ICFs
- SUBMISSION OF REVISED SITE ICFs IN RESPONSE TO A DISAPPROVAL NOTIFICATION.

Site-specific ICF(s) must contain all information necessary to comply with U.S. federal regulations, local laws and regulations, ICH and DAIDS policies. This includes all the basic and additional elements, as outlined in U.S. federal regulations, 45 CFR 46.116 and 21 CFR 50.25. To assist sites with developing their site-specific ICF(s), DAIDS works with the Protocol Teams to create sample ICFs that contain all the specific elements required by the U.S. federal regulations, 45 CFR 46.116 and 21 CFR 50.25.

A CRS must submit to the DAIDS PRO a copy of all site-specific ICF(s) that will be used during the informed consent process at the site after review and approval by the IRB/EC and other applicable Regulatory Entity (RE)/Regulatory Authority(ies). and retain the original(s) on file at the site.

All materials that are used in the informed consent process (e.g., ICFs, questionnaires, etc.) that are given to participants should be submitted to DAIDS for sponsor files along with any approvals (if any) IRB/EC/ RE of these documents.

If there any Sample ICFs provided with the final DAIDS approved version of the protocol that will *not* be needed at a CRS, (i.e., if a pregnancy ICF is not needed because pregnant women will not be enrolled), the CRS must document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with the registration submission.

If a Sample ICF is removed as part of an amended protocol and the site will no longer be using the consent form, a memo or note must be included with the Amendment registration submission declaring that the specific consent form will no longer be utilized at the site.

When an IRB/EC/ RE/Regulatory Authority(ies). approves a site-specific ICF and the site contact information is left blank, the CRS must include a memo with their registration submission explaining that the CRS will insert the site-specific contact information prior to consenting participants.

If an IRB/EC/RE/Regulatory Authority(ies) requires language in a site-specific ICF specific to the institution or based on local regulations/requirements, the site should include that information in the site-specific ICF and must provide documentation from IRB/EC/RE regarding the required language in the site-specific ICF. However, even though an IRB/EC/RE requires language in site-specific ICF, none of the basic and additional elements found in the DAIDS approved Sample ICF or required by DAIDS policy should be removed. Refer to the Frequently Asked Questions and the Informed Consent Process Information on the DAIDS RSC website for additional information regarding the development of site-specific ICFs.

If a CRS deletes or makes any substantive change to basic and/or additional elements as presented in the DAIDS-approved Sample ICF, the IOR or designee for the clinical trial must provide written documentation to explain the deletions/change(s) at the time of registration submission to the DAIDS PRO.

All site-specific ICF(s) must be able to be linked to the current DAIDS approved version of the protocol. The DAIDS-required identifying information are:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols which include both on the DAIDS-approved Sample ICF forms.

- DAIDS ES and/or Network Protocol ID Number.

- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS and/or the final version date of the protocol document approved by DAIDS.

NOTE: *For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable REs/Regulatory Authority(ies)), CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the DAIDS protocol version number and/or the final version date of the DAIDS-approved protocol must remain on all site-specific ICFs as well.*

NOTE: *If any of the site-specific ICF(s) do not contain enough information to be linked to the most current DAIDS-approved version of the protocol, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

J. Types of ICFs and Protocol Registration Requirements

Main ICF - The Main ICF issued for enrollment of participants into the protocol. The Main ICF should include all of the basic and appropriate additional elements as outlined in U.S. federal regulations, 45 CFR 46.116 and 21 CFR 50.25. The link to OHRP's guidance on informed consent form required elements can be found here.

Screening and Stored Specimen ICFs - The following are DAIDS requirements regarding generic screening and stored specimen consent forms and protocol- specific screening consent forms.

Generic screening and stored specimen ICF - A generic screening and/or stored specimen ICF is an ICF that is developed by a CRS for its own purposes and not related to any DAIDS requirement and should NOT be submitted to the DAIDS PRO. The DAIDS PRO will NOT review or approve any such generic screening and/or stored specimen ICFs if they are submitted with registration materials.

Protocol-specific screening and stored specimen ICF - A protocol-specific screening and/or stored specimen ICF is an ICF developed for a specific protocol that is approved by DAIDS and is included as part of the final protocol and DAIDS-approved Sample ICFs. If the DAIDS-approved Main ICF includes screening procedures and stored specimen information and a CRS chooses to develop a separate protocol-specific screening and/or stored specimen ICF to be used at the site, then the screening and eligibility and/or stored specimen information can be removed from the site-specific main ICF. In this instance, the CRS must submit BOTH the protocol-specific screening and/or stored specimen ICF and the site-specific main ICF to the DAIDS PRO for review and approval.

Short ICFs - If a CRS elects to use a short ICF in addition to the main ICF, the CRS must have a main ICF OR written summary that includes all the required basic and appropriate additional elements which have been approved by the IRB/EC and has been submitted to the DAIDS PRO for registration. A CRS must receive a Registration Notification from the DAIDS PRO for all short form ICFs prior to implementation.

Sub-study ICFs - If a NIAID (DAIDS)-supported and/or-sponsored protocol includes a separate DAIDS-approved Sample ICF for a sub-study that is part of the main protocol and the CRS anticipates participating in the sub-study, the CRS must include the sub-study site-specific ICF in their protocol registration submission. A CRS must receive a Registration Notification from the DAIDS PRO for all sub- study ICFs prior to implementation.

Pregnancy ICF - If a DAIDS-supported and/or sponsored protocol includes a DAIDS-approved Sample ICF for women who become pregnant while on study and the CRS anticipates that some pregnant women may be included or followed on the study, the CRS must submit the site-specific pregnancy ICF to the DAIDS PRO.

Sites have the flexibility to combine the pregnancy ICF and the main ICF into one ICF, as long as the required information is still present, and this approach is approved by the IRB/EC. If one or more ICFs are combined, there should be a note to the DAIDS PRO documenting why one of the original consents is not included in the registration submission.

If the site will not follow or enroll pregnant women, the pregnancy ICF does not need to be submitted, and the site should document the plan not to include pregnant women with a note to the DAIDS PRO. A CRS must receive a Registration Notification from the DAIDS PRO for any pregnancy ICF prior to implementation.

Assents - The IRB/EC must determine that adequate provisions are made for soliciting the assent of children and/or adolescents when in the judgment of the IRB/EC the children and/or adolescents are capable of providing it, 45 CFR 46.408. The IRB/EC is responsible for determining the age of assent and for determining whether the use of an assent form is appropriate. A CRS must receive a Registration Notification from the DAIDS PRO for all assents prior to implementation.

1. Health Insurance Portability and Accountability Act (HIPAA) - Privacy Rule

The Privacy Rule is a U.S. federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information.

The DAIDS PRO does not review site-specific ICFs for information related to HIPAA. If the site-specific ICF(s) contains language pertaining to HIPAA authorization, the DAIDS PRO will NOT assess this language for Privacy Rule compliance.

In addition, it is very important that confidentiality language included in the DAIDS-approved sample informed consent remain in the site-specific ICF even if this information is included in a separate HIPAA authorization form.

NOTE: *The HIPAA regulations do not apply to non-U.S. CRSs.*

Information related to the Privacy Rule can be found at the following HHS website.

2. ClinicalTrials.gov Informed Consent Requirements

ClinicalTrials.gov is the clinical trial registry databank maintained by the NIH National Library of Medicine (NLM) which was created by statute outlined in the Food and Drug Administration Amendments Act of 2007 (FDAAA). Through FDAAA, the U.S. Food and Drug Administration (FDA) amended current informed consent regulations (21 CFR 50.25) to now require that all informed consent documents for applicable drug (including biological products) and device clinical trials include a specific statement that clinical trial information will be entered into ClinicalTrials.gov. As of December 1, 2011, for new protocols, the following language **MUST** be included in the DAIDS-approved sample ICF for applicable trials:

"A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time."

The DAIDS PRO will review site-specific ICFs for information related to clinicaltrials.gov. If the DAIDS-approved Sample ICF contains the clinicaltrials.gov language, then the language MUST be in all site-specific informed consents for that study. Failure to include this language exactly as stated above in all applicable Site ICFs will result in an Approval with Required Corrections notification.

NOTE: *Per U.S. federal regulations, this language cannot be modified.*

NOTE: *Participants do not need to be re-consented for existing or ongoing studies unless the IRB/EC determines otherwise.*

NOTE: *The required language can be translated into local language.*

NOTE: *If the inclusion of the ClinicalTrials.gov language is mandated by the IRB/EC/RE (for non-applicable trial), documentation from the IRB/EC/Regulatory Authority mandating the statement inclusion must be provided to the DAIDS PRO.*

Information related to the informed consent requirement for clinicaltrials.gov can be found on the following HHS website.

K. Translation requirements

For all documents that require translation to a language other than Spanish, a CRS must submit to the DAIDS PRO a copy of the DAIDS Protocol Registration Translation Confirmation Document, attesting that the translation is a true and accurate reflection of the local language documents that have been reviewed and approved by the IRB/EC and other REs/Regulatory Authority.

In addition, sites must submit a translation certificate or its equivalent (i.e., a signed and dated documentation by the translator/translators attesting that the translation is a true and accurate interpretation of the local language document).

NOTE: CRSs are not required to complete the DAIDS Protocol Registration Translation Confirmation Document for any protocol registration documents in Spanish.

An electronic copy of the DAIDS Translation Confirmation Document can be found on the DAIDS RSC Website under the "Protocol Registration" section.

1. Form FDA 1572, IOR Form, CVs, and Medical Licenses

All Form FDA 1572s, DAIDS IOR Forms, CVs and Medical Licenses must be prepared in English. Non-English versions of these documents will not be accepted by the DAIDS PRO.

2. IRB/EC, other RE/Regulatory Authority, and IBC approval letters

All non-English IRB/EC, other applicable RE/Regulatory Authority, and IBC approval letter(s) must be translated into English, except for Spanish. CRSs must submit copies of both the local language and translated English approval letter(s) to the DAIDS PRO.

NOTE: *CRSs should provide an English translation of any other appropriate IRB/EC/RE/IBC documentation that explains changes/deletions in the site specific ICFs or that could assist the DAIDS PRO when reviewing registration materials.*

3. Site-specific ICFs

CRSs must prepare site-specific ICFs in all languages in which they will conduct informed consent discussions for each study. If CRSs elect to use short ICFs in addition to the Main ICF, the short ICF must also be prepared in all languages in which the informed consent discussions will be conducted. After approval by all applicable IRBs/ECs and REs, copies of the approved site-specific ICFs must be submitted to the DAIDS PRO.

If informed consent discussions will be conducted in English and another local language, including Spanish, the site-specific English and local language ICFs must be submitted to the DAIDS PRO. No back-translations are required by DAIDS.

If informed consent discussions will be conducted in a local language other than English or Spanish, site-specific local language ICFs must be submitted to the DAIDS PRO. Back-translations (into English) of the site-specific local language ICFs for which discussion will be conducted also must be submitted to the DAIDS PRO.

NOTE: *If a DAIDS Clinical Trials Network has specific requirements regarding translation of site-specific ICFs, the CRS should follow those requirements as well as any applicable translation and back-translation requirements specified in institutional policies, the study protocol, and/or the network Manual of Operations.*

NOTE: *Site specific ICFs in languages that were not submitted with the original initial registration should be submitted as additional ICF language type within DPRS and will be considered initial registration in the newly submitted language type.*

4. Clinical Trial Application (CTA) Form/Document

All non-English Clinical Trial Application Form/Documentation must be translated into English, except for Spanish. Copies of both the local language and translated English applications must be submitted to the DAIDS RSC along with the translation certificate and the Translation Confirmation Document (TCD).

VI. Protocol Registration Submissions

Prior to implementing a protocol and enrolling participants, a CRS must receive final approval for the site-specific ICFs from the IRB/EC and other applicable REs/Regulatory Authority(ies). In addition, the CRS must successfully complete the DAIDS initial protocol registration process. However, successfully completing the DAIDS initial protocol registration process does not authorize a CRS to begin enrollment of participants. CRSs will be notified by the appropriate DAIDS scientific program (i.e., Program Officer), Operations Center or Data Management Center when enrollment may begin for a protocol.

Each CRS will complete the protocol registration process for all clinical research supported and/or sponsored by DAIDS that is reviewed by DAIDS Scientific Review Committees, namely the Prevention Sciences Review Committee (PSRC) and the Clinical Sciences Review Committee (CSRC) and if it is determined protocol Registration is required. Upon receiving final IRB/EC and other applicable RE/Regulatory Authority approval(s), the CRS will submit all required registration documents to the DAIDS PRO via the DAIDS DPRS.

Upon making ANY submission to the DAIDS PRO, a CRS will receive a Confirmation of Submission notice that indicates successful submission of materials to the DAIDS PRO. If a CRS does not receive a Confirmation of Submission notice within 24 - 48 hours of submitting materials, the CRS should contact the DAIDS PRO.

The CRS must place a copy of all final Protocol Registration notifications from the DAIDS PRO in the site's regulatory files. Refer to Definitions of this manual for a list of final registration notifications.

A. Initial Registration

A CRS that has **not previously** received a Registration Notification from the DAIDS PRO for any version of the protocol must complete the initial protocol registration process.

If a CRS has previously received a DAIDS PRO Registration Notification for one language (i.e., English) and later submits registration documents for a new language (i.e., Spanish), the new language should be submitted as an Additional ICF Language submission type but will be considered an initial registration as this is the first time the specific language has been submitted to the DAIDS PRO for review.

If a CRS has previously received a Registration Notification from the DAIDS PRO for one informed consent type (e.g., main, pregnancy) and later submits registration documents for a new informed consent type (e.g., stored specimen, short form), the new informed consent type should be submitted as an Additional ICF Type but is considered an initial registration as this is the first time the informed consent form has been submitted to the DAIDS PRO for review.

NOTE: *If a CRS has previously received a Registration Notification from the DAIDS PRO and is only submitting an additional language or informed consent type, the site is NOT required to resubmit the Form FDA 1572/DAIDS IOR Form and the IOR CV with the protocol registration submission.*

The following documents **must** be submitted to the DAIDS PRO for all initial registration submissions:

- A copy of the Form FDA 1572 signed and dated by the IOR (for studies conducted under an IND) OR a copy of the DAIDS IOR Form signed and dated by the IOR (for non-IND studies).
- Investigator of Record CV and other required documentation
  (current medical license or equivalent).
- Protocol Signature Page (PSP).
- A copy of the CRS's IRB/EC and other applicable RE/Regulatory Authority approval letter(s)
  (see IRB/EC Approvals" of this manual)
- A copy of the IRB/EC and other applicable RE/Regulatory Authority approved site-specific ICFs (all languages including English translations, if applicable). Refer to Translation requirements" of this manual.
- A copy of the CRS's IBC approval letter, if applicable.
- Clinical Trial Application Form/Document for the site and study
- A copy of the CRS's IRB/EC/Regulatory Authority submission letter(s).
- A copy of all correspondence between the CRS and IRB/EC/Regulatory Authority
- Translation Certificate (if applicable).
- Translation Confirmation Document (if applicable).

NOTE: *If an initial registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual. Not submitting all documentation may delay registration.*

When all required documents have been received and reviewed, a CRS will receive a Registration Notification from the DAIDS PRO that will include all languages and informed consent types that have been submitted. The Registration Notification from the DAIDS PRO indicates successful completion of the initial protocol registration process.

If a CRS receives a Registration with Required Corrections Notification, a CRS must make the required corrections and submit them to their IRB/EC for review and approval OR must submit justification for why the required correction(s) will not be made to the DAIDS PRO within 120 calendar days of the date the Required Corrections Notification was issued. For information on how to submit required corrections refer to Registrations with Required Corrections" of this manual.

NOTE: *The 120 calendar days is for submission of IRB/EC approved corrections OR justifications for why the corrections will not be made to the DAIDS PRO.*

Upon successful completion of the DAIDS PRO initial registration process, indicated when a CRS receives a Registration Notification or a Registration with Required Corrections Notification, a CRS will begin receiving safety information for the protocol (i.e., safety reports, safety memos, investigator's brochures, etc.) from the DAIDS RSC Safety Information Center.

If a site-specific ICF(s) does not include all the required basic and appropriate additional elements to comply with U.S. Federal Regulations and DAIDS policies, designated CRS personnel (i.e., CRS Coordinator, IOR) will be notified via a Disapproval Notification from the DAIDS PRO regarding the deficiencies. The Disapproval Notification will outline the deficiencies in the site-specific ICF(s) that must be revised/corrected before a final Registration Notification can be issued.

NOTE: *A Disapproval Notification is not a final notification and DOES NOT indicate successful completion of the protocol registration process.*

For information on the options a CRS has upon receipt of a Disapproval Notification from the DAIDS PRO, refer to VI of this manual.

B. Amendment Registrations

1. Full Version Protocol Amendment Registration

A full version "Protocol Amendment" is a revision to a protocol made by the Protocol Team/Chair/Awardee that requires DAIDS review and final approval/sign-off before implementation. The changes to the protocol are incorporated into the protocol document and will result in a change to the DAIDS protocol version number (e.g., 2.0, 3.0). Sites should refer to the protocol document for information on the protocol registration process for full version protocol amendments.

CRSs should submit the amended protocol, DAIDS-approved Sample ICF(s), and the amended site-specific ICF(s) to their IRBs/ECs/REs and other applicable Regulatory Authority(ies) for review and approval as soon as possible. Per the DAIDS Protocol Registration policy, submission to the reviewing IRB/EC must take place within 45 calendar days for U.S. sites and 75 calendar days for non-U.S. sites of the date the amendment was approved by DAIDS and distributed to the sites.

NOTE: *The 45 or 75 calendar day requirement for submission of full version protocol amendment registration materials is for reviewing IRB/EC only.*

Amendments including any revised site-specific ICF(s) must be implemented immediately (i.e., without delay no later than 5 business days, usually at the participant's next scheduled study visit) upon CRS receipt of all required IRB/EC/ RE/Regulatory Authority(ies)approvals unless the amendment specifies otherwise. DAIDS PRO approval notification is not required for amendments unless specified in the protocol.

The CRS may delay implementing an amendment when the IRB/EC/ RE/Regulatory Authority(ies) approved amendment states the protocol changes will be implemented once specific operational issues (i.e., training on new procedures added in the amendment) are addressed. The IRB/EC/ RE/Regulatory Authority(ies) documentation must be kept in the site's regulatory files for verification by monitors.

When the IRB/EC/ RE/Regulatory Authority(ies) approved amendment and revised site-specific ICFs are not implemented immediately after final IRB/EC/ RE/Regulatory Authority(ies) approval, sites may continue conducting protocol related interactions and interventions with already enrolled study participants under the previously approved version as long as the IOR has determined that this is in the participant's best interest. After receiving final IRB/EC/ RE/Regulatory Authority(ies) approval and while operational issues are being addressed, new participants may only be enrolled under the previously approved version of the site-specific ICFs when the IRB/EC/RE/Regulatory Authority(ies). has determined this is acceptable. The IRB/EC/ RE/Regulatory Authority(ies) determination should be documented in writing and filed in the site's regulatory files.

A CRS must submit full version protocol amendment registration documents to the DAIDS PRO within 14 calendar days of the CRS's receipt of all the required final written IRB/EC approval documentation for the amendment. The submitted documents must include documentation of the date the amended protocol and any revised site-specific.

NOTE: *Sites are strongly advised to document the date the CRS receives each final* IRB/EC/ RE/Regulatory Authority(ies) *approval letter. Documenting this information supports the CRS's action to comply with the DAIDS protocol registration policy regarding submission of amendment and LOA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final* the IRB/EC/RE/Regulatory Authority(ies) *approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.*

If a CRS has received a Registration Notification from the DAIDS PRO for an earlier version of the protocol including all informed consent types and specific language(s), then the registration to a new version of the protocol would be a full version protocol amendment. A CRS that has never received a Registration Notification from the DAIDS PRO for any version of the protocol, language or informed consent type must follow the instructions for Initial Registration of this manual.

NOTE: *If a CRS has submitted a registration packet for a previous version of a protocol prior to a new version being approved by DAIDS and distribution to the sites, the DAIDS PRO will continue to process the registration for the earlier version.*

The following documentation must be submitted to the DAIDS PRO for all full version protocol amendment registration submissions:

- A copy of the site's IRB/EC and other applicable RE/Regulatory Authority approval letter(s)

Refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual for detailed information.

- Documentation of the date the amended protocol and any revised site- specific ICF(s) were submitted to the reviewing IRB/EC.

- Protocol Signature Page (PSP) to document the commitment of the IOR(s) to conduct the trial in compliance with regulations/laws.

- A copy of the IRB/EC/RE and other applicable Regulatory Authority (ies) approved site ICF(s) (all languages including English translations, if applicable). Refer to section V, "Translation Requirements" of this manual.

- A copy of the CRS's IBC approval letter, if applicable

- Any amended (if applicable) in-country Clinical Trial Application Form/Document for all applicable entities. See the Clinical Trial Application Submission Guidance on DAIDS RSC website for additional information.

- A copy of the CRS's IRB/EC and other applicable /Regulatory Authority(ies) submission letter(s).

- A copy of all correspondence between the CRS and IRB/EC and other applicable RE/Regulatory Authority(ies).

- Translation Certificate (if applicable).

- Translation Confirmation Document (if applicable).

NOTE: *If any Site Specific ICFs registered in the previous version will no longer be utilized at the site, documentation must be submitted that states that the Site Specific ICFs will no longer be utilized at the site.*

NOTE: *Examples of appropriate documentation of the date the amended protocol and any revised site-specific ICF(s) were submitted to the reviewing IRB/EC includes but is not limited to the submission letter from the site to the IRB/EC, a memo from the IOR or designee specifying the date of submission to the IRB/EC.*

NOTE: *If the IRB/EC determines that a full version protocol amendment does not require changes to the site-specific ICF(s), the CRS should document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with the full version protocol amendment registration submission. Otherwise, all previously registered Site Specific ICF types must be submitted with the amended version or Justification for the omission of Site Specific ICF type must be provided. Documentation of approval of the amended protocol is still required from of the site's IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s) and any other appropriate documentation from the IRB/EC and other applicable RE/Regulatory Authority(ies) regardless of whether the site specific ICFs were revised.*

NOTE: *Re-consenting participants as a result of amendment (Change or new information that may affect subject participation) is the decision of the CRS's IRB/EC. CRSs should follow their IRB/EC/RE/ Regulatory Authority instructions for re- consenting participants as a result of a full version protocol amendment. For additional information regarding re-consenting see the DAIDS Memo Regarding Timing of Consent and Re-Consent with Updated IRB/EC/RE-Approved Consent Forms on the DAIDS RSC website Site Informed Consent Process Information.*

NOTE: *If a full version protocol amendment registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to "Requested Materials" of this manual.*

When all required documents have been received and approved, a CRS will receive a Registration Notification from the DAIDS PRO that will include all languages and informed consent types that have been submitted. The Registration Notification from the DAIDS PRO indicates successful completion of the full version protocol amendment registration process.

NOTE: *A Registration Notification from the DAIDS PRO is NOT required prior to implementing a full version protocol amendment at a CRS.*

NOTE: *Once a new version of a protocol is approved by DAIDS and has been distributed to the sites, a CRS will no longer be able to register for a previous version.*

2. Letter of Amendment (LOA) Registration

CRSs should submit the LOA and any amended site-specific ICF(s) to their IRBs/ECs and other applicable REs/ Regulatory Authority (ies) for review and approval as soon as possible. Per the DAIDS Protocol Registration policy, submission to the reviewing IRB/EC must take place within 45 calendar days for U.S. sites and 75 calendar days for non-U.S. sites of the date the LOA was approved by DAIDS and distributed to the sites.

NOTE: *The 45 or 75 calendar day requirement for submission of LOA materials is for reviewing*
IRB/EC only.

NOTE: *Protocol revisions resulting from LOAs DO NOT affect the DAIDS protocol version. For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable Regulatory Authority(ies)/Regulatory Authority(ies), CRSs can specify the site (local version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the DAIDS protocol version number and/or the final version date of the DAIDS-approved protocol should remain on all site-specific ICFs.*

LOAs including any revised site-specific ICF(s) must be implemented immediately (i.e. without delay no later than 5 business days, usually at the participant's next scheduled study visit) upon a CRS' receipt of all required IRB/EC and RE/ Regulatory Authority approvals DAIDS PRO approval notification is not required for LOA unless specified in the LOA.

The CRS may delay implementing a LOA when the IRB/EC/ Regulatory Authority (ies)/Regulatory Authority(ies) approved LOA states the protocol changes will be implemented once specific operational issues (i.e., training on new procedures added in the LOA) are addressed. The IRB/EC/RE/Regulatory Authority(ies) documentation must be kept in the site's regulatory files for verification by monitors.

When the IRB/EC/ RE/Regulatory Authority(ies) approved LOA and revised site-specific ICFs are not implemented immediately after final IRB/EC/RE approval, sites may continue conducting protocol related interactions and interventions with already enrolled study participants under the previously approved version as long as the IOR has determined that this is in the participant's best interest. After receiving final IRB/EC/ RE/Regulatory Authority(ies) approval and while operational issues are being addressed, new participants may only be enrolled under the previously approved version of the site-specific ICFs when the

IRB/EC/RE has determined this is acceptable. The IRB/EC/ RE/Regulatory Authority(ies) determination should be documented in writing and filed in the site's regulatory files.

A CRS must submit LOA registration documents to the DAIDS PRO within 14 calendar days of the CRS's receipt of all the required final written IRB/EC approval documentation for the LOA. The submitted documents must include documentation of the date the LOA and any revised site-specific ICF(s) were submitted to the reviewing IRB/EC. The DAIDS PRO will not review any revised site-specific ICF(s) unless otherwise noted in the LOA.

NOTE: *Sites are strongly advised to document the date the CRS receives each final IRB/EC/ RE/Regulatory Authority(ies) approval letter. Documenting this information supports the CRS's action to comply with the DAIDS protocol registration policy regarding submission of amendment and LOA registration materials to the DAIDS PRO within 14 calendar days of receipt of all final IRB/EC/ RE/Regulatory Authority(ies) approval letters. This documentation should be kept in the site's regulatory files for verification by monitors.*

The following documentation must be submitted to the DAIDS PRO for all LOA registration submissions:

- A copy of the site's IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s)for all Entity(ies) listed on the FDA Form 1572/DAIDs IOR Form (refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual for detailed information on IRB/ RE/Regulatory Authority(ies))

- Documentation of the date the LOA and any revised site-specific ICF(s) were submitted to the reviewing IRB/EC.

- Protocol Signature Page (PSP) to document the commitment of the IOR(s) to conduct the trial in compliance with regulations/Laws

- A copy of the IRB/EC and other applicable RE/Regulatory Authority(ies) approved site ICF(s) (all languages including English translations, if applicable). Refer to Translation requirements" of this manual.

- A copy of the CRS's IBC approval letter, if applicable.

- A copy of the CRS's IRB/EC and other applicable RE/ Regulatory Authority submission letter(s).

- A copy of all correspondence between the CRS and IRB/EC and other applicable RE/Regulatory authorities.

- Translation Certificate (if applicable).

- Translation Confirmation Document (if applicable).

NOTE: *Examples of appropriate documentation of the date the LOA and any revised site-specific ICF(s) were submitted to the reviewing IRB/EC includes but is not limited to -*

- *the submission letter from the site to the IRB/EC.*
- *a memo from the IOR or designee specifying the date of submission to the IRB/EC.*

NOTE: *Re-consenting participants as a result of LOA (Change or new information that may affect subject participation) is the decision of the CRS's IRB/EC. CRSs should follow their IRB/EC/ RE/Regulatory Authority(ies)instructions for re- consenting participants as a result of the LOA.*

NOTE: *If a LOA registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

When all required documents have been received, a CRS will receive a Registration Notification from the DAIDS PRO for each LOA registration submission. The Registration Notification from the DAIDS PRO indicates successful completion of the LOA registration process.

NOTE: *LOAs are considered individual amendments to a protocol. Thus, sites must protocol register to all LOAs independent of initial and full version amendment registrations. If a site elects to include a LOA as part of another submission to the IRB/EC/ RE/ Regulatory Authority(ies) (i.e., continuing review, amendment review, and initial review) the site must clearly document all the materials that are being submitted to the IRB/EC/ RE/Regulatory Authority(ies) for review and approval. It is a CRS's responsibility to inform the DAIDS PRO regarding all registrations (i.e., LOA, full version amendment, initial, continuing review) the site is requesting at the time of submission. Failure to register to a LOA may result in a CRS being out of compliance with DAIDS policies and may result in delays in implementing operational changes triggered by LOA registrations.*

NOTE: *All submission types (Initial, Full Version Amendment, LOA) must be submitted independently.*

NOTE: *A Registration Notification from the DAIDS PRO is NOT required prior to implementing a LOA at a CRS.*

C. Sub-Study Registration

A CRS must protocol register to all sub-studies that have a protocol number and/or DAIDS protocol identification number if a site anticipates enrolling participants. A CRS will receive a registration notification for each sub-study that is submitted for protocol registration. CRSs must register to embedded sub-studies as part of the main study registrations. Registration for embedded sub-studies is required for all versions of the main study unless the site informs the DAIDS PRO that they are no longer participating in the embedded sub-study and request deregistration. CRSs should register to stand alone sub-studies as separate registrations and can be done independently from the main study registration. A CRS registering to a stand-alone sub-study is required to submit all required documents (i.e., IRB/EC approval letter(s), site-specific consent(s), Form FDA 1572 and/or DAIDS IOR Form, and IOR CV) when registering to a stand- alone sub-study.

NOTE: *For an explanation of embedded and stand-alone sub-studies refer Definitions of this manual.*

D. Other Submissions

Other submissions are ANY submissions made to the DAIDS PRO that are not Initial, Full Version Amendment or LOA registrations. Below is detailed information on requirements related to "other submissions" a CRS may submit to the DAIDS PRO.

1. Requested Materials

Requested materials are additional and/or corrected materials requested by the DAIDS PRO as a result of an incomplete submission to the DAIDS PRO. If any required documents are missing, incomplete, or are inaccurate, the DAIDS PRO will issue a Requested Materials notice to designated CRS personnel (i.e. CRS Coordinator, IOR). ***This request will stop the registration review process.***

NOTE: *The Protocol Registration review process will not continue until all Requested Materials have been received by the DAIDS PRO.*

A copy of the requested materials must be submitted to the DAIDS PRO in response to a Materials Request Notification as a "materials Request" type submission.

A CRS will receive a Confirmation of Submission notice once the requested materials have been received by the DAIDS PRO.

2. Disapprovals

If it is determined during the DAIDS PRO review process that a site-specific ICF(s) does not include all the required basic and appropriate additional elements to comply with Federal Regulations and DAIDS policies, designated CRS personnel (e.g., CRS Coordinator, IOR)

will be notified via a Disapproval Notification from the DAIDS PRO regarding the deficiencies. The disapproval notification will outline the deficiencies in the site-specific ICF(s) that must be revised or corrected before a final Registration Notification can be issued.

Upon receipt of a Disapproval Notification from the DAIDS PRO a CRS has two options:

1. Make the necessary revisions/corrections and submit the revised document(s) to their IRB/EC and other applicable RE/Regulatory Authority(ies) approval(s) for review and approval. Upon receiving final IRB/EC/ RE/Regulatory Authority(ies) approval for the revised document(s) the CRS must make a "Corrected Materials" submission to the DAIDS PRO, or

2. Submit justification for the omission/changes to the DAIDS PRO via a request for Disapproval Reversal.

Under Option 1 - The following documentation must be submitted to the DAIDS PRO as “Corrected Materials” once a CRS receives final IRB/EC and other applicable RE/ Regulatory Authority approval for the revised document(s) -

- A copy of the site’s IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s) and any other appropriate documentation from the IRB/EC other applicable REs/ Regulatory Authority (ies).

  NOTE: *For examples of other appropriate IRB/EC/RE/Regulatory Authority(ies) documentation refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals” of this manual.*

- A copy of the IRB/EC and other applicable RE/Regulatory Authority(ies) approved revised site-specific ICF(s).

When ALL required documents have been received and it is confirmed that the required corrections have been made, the DAIDS PRO will issue a Registration Notification.

Under Option 2 - If a CRS believes that a Disapproval Notification has been issued in error, the CRS can submit a request for Disapproval Reversal. A CRS must provide justification and/or documentation explaining why the disapproval should be reversed.

The following documentation must be submitted to the DAIDS PRO to request a disapproval reversal:

- Written justification and/or a copy of any documentation supporting the CRS’s request for the disapproval reversal

A CRS will be notified within 4 business working days as to whether or not the disapproval will be reversed via e-mail from the DAIDS PRO.

3. Registrations with Required Corrections

If a CRS receives a Registration with Required Corrections Notification, a CRS must make the required corrections and submit them to their IRB/EC/ RE/Regulatory Authority(ies) for review and approval OR must submit justification for why the required corrections will not be made within 120 calendar days of the date the Registration with Required Corrections Notification was issued.

A Registration with Required Corrections Notification indicates that a CRS may begin using the site-specific ICFs after protocol activation by the appropriate Operations Center, Data Management/Statistical Center or DAIDS Program.

Upon receipt of a Registration with Required Correction Notification from the DAIDS PRO a CRS has two options:

1. Make the necessary required corrections and submit them to their IRB/EC for review and approval. Upon receiving final IRB/EC and other applicable RE/Regulatory Authority(ies) approval for the corrected document(s) the CRS must make a "Corrected Materials" submission to the DAIDS PRO, or

2. Submit justification for the omission/changes via a "Corrected Materials" submission to the DAIDS PRO.

Under Option 1 - The following documentation must be submitted to the DAIDS PRO as “Corrected Materials”, once a CRS receives final IRB/EC and other applicable RE/Regulatory Authority(ies) approval for the corrected document(s):

- A copy of the site’s IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s) and any other appropriate documentation from the IRB/EC other applicable RE/Regulatory Authority(ies).

- A copy of the IRB/EC and other applicable RE/Regulatory Authority(ies) approved revised/corrected site-specific ICF(s).

NOTE: *For examples of other appropriate IRB/EC/ RE/Regulatory Authority(ies) documentation refer to IRB/EC Approvals” of this manual.*

Under Option 2 - If a CRS has believed that a Registration with Required Corrections Notification has been issued in error, the CRS can submit justification and /or documentation explaining why the Registration with Required Corrections Notification should be reversed.

The following documentation must be submitted to the DAIDS PRO as “Corrected Materials”:

- Written justification and/or a copy of any documentation supporting the CRS’s request for the Registration with Required Corrections reversal.

For Option 1 and 2, a CRS will receive an Approval of Required Corrections Notification from the DAIDS PRO when all the required corrections have been reviewed and approved. The official registration date will remain the date the Registration with Required Correction Notification was issued.

4. Administrative Registration

Administrative registrations should occur when a site is not recruiting participants in a NIAID (DAIDS)-supported and/or -sponsored clinical trial but has administrative functions only. Protocol/Grant PI/Protocol Chair/Co-Chair’s routinely make substantial study interventions (decisions and interpretations) that affect study participants even though participants may not be enrolled or seen at the Protocol/Grant PI/Protocol Chair/Co-Chair’s CRS. As a result, the Protocol/Grant PI/ Protocol Chair/Co-Chair’s institutions are considered engaged with the research and must assure compliance with applicable Department of Health and Human Services (DHHS) regulations. For more information on engagement refer to the OHRP guidance document.

Based on U.S. federal regulation 45 CFR 46.103(a), “each institution engaged" in human subject research that is supported and/or sponsored by the DHHS must provide the OHRP with a satisfactory Assurance of Compliance with the regulations, unless the research is exempt under U.S. federal regulation 45 CFR 46.101(b).

For all administrative registrations, DAIDS requires that that the Protocol/Grant PI/Protocol Chair/Co-Chair consults with their IRB/EC and receive documentation in writing of the IRB/EC's decision concerning their protocol review and approval. At least two different kinds of decisions can be made:

1. IRB/EC wants to be involved in reviewing and approving the protocol.

2. IRB/EC does not want to be involved in reviewing and approving the protocol and will rely on another IRB/EC, designated on the Federal Wide Assurance (FWA), for review and approval.

DAIDS will honor the decision of the IRB/EC. The Protocol/Grant PI/ Protocol Chair/Co-Chair (s) need to consult with their IRB/EC and obtain written documentation of the IRB/EC's decision regarding their review and approval of the protocol in order to comply with U.S. federal regulations.

Upon receipt of final approval and/or documentation from the IRB/EC, an administrative registration submission should be made to the DAIDS PRO.

The following documentation must be submitted to the DAIDS PRO for all Administrative Registrations:

- A copy of the IRB/EC approval letter *AND* any other appropriate documentation from the IRB/EC including the IRB/EC decision regarding protocol review and approval.

  NOTE: *For examples of other appropriate IRB/EC/ RE/Regulatory Authority(ies) documentation refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual.*

- A copy of the Form FDA 1572 signed and dated by the Protocol/Grant PI/Protocol Chair/Co-Chair (for studies conducted under an IND) OR a copy of the DAIDS IOR Form signed and dated by the Protocol Protocol/Grant PI/ Protocol Chair/Co-Chair (for non-IND studies)

- A copy of the Protocol/Grant PI/Protocol Chair/Co-Chair CV and corresponding Medical license/equivalent

A CRS will receive a Registration Notification from the DAIDS PRO for each administrative registration submission when all required documents have been received. The Registration Notification from the DAIDS PRO indicates successful completion of the administrative registration process.

5. Change of Investigator of Record (IOR)

When there is a change in the IOR listed in Section 1 on the Form FDA 1572 or DAIDS IOR Form, a CRS should submit a copy of the revised Form FDA 1572 or the revised DAIDS IOR Form to the DAIDS PRO. To officially change the IOR for a protocol(s), the CRS must submit the documentation within 15 calendar days of the CRS's notification that the current IOR will no longer serve as the IOR for the study. CRS must notify DAIDS when there is a change of IOR in a timely manner.

The following documentation should be submitted to the DAIDS PRO for all Change of IOR requests:

- Memo requesting a change of IOR.
- A copy of the new Form FDA 1572 signed and dated by the new IOR (for studies conducted under an IND) OR a copy of the new DAIDS IOR Form signed and dated by the new IOR (for non-IND studies).
- CV for the new IOR and other required documentation (current medical license or equivalent).
- A Protocol Signature Page for the new Investigator of Record.
- If IRB/EC or RE/Regulatory Authority(ies) approval is required to change the investigator at the CRS, the submission and approval letters from the entity(ies) is required.

A CRS will receive a Change of IOR Approval Notification from the DAIDS PRO when the change of IOR has been reviewed and approved by the DAIDS PRT.

NOTE: *The Change of IOR is NOT official until the CRS receives a Change of IOR Approval Notification from the DAIDS PRO.*

NOTE: *A CRS must notify their DAIDS Office for Clinical Site Oversight (OCSO) representative and/or DAIDS Program Officer when there is a change in CRS Leader or other key CRS site personnel and/or contact information.*

6. Continuing/Annual Review

Per the October 2018 FDA Guidance on FDA-Regulated Clinical Investigations (studies under an IND), IRB/ECs must continue to comply with current FDA requirements for IRB/ECs continuing review at 21 CFR 56.109(f), including for clinical investigations that are subject to both HHS and FDA jurisdiction. IRB/ECs are required to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (21 CFR 56.109(f)).

For studies that are NOT conducted under an IND, DHHS regulations, 45 CFR 46.109(e) require that all DHHS supported research undergo continuing IRB/EC review at intervals appropriate to the degree of risk, but NOT LESS than once per year.

As described in §46.109(f)(1)

Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research eligible for expedited review in accordance with §46.110;

(ii) Research reviewed by the IRB in accordance with the limited IRB review described in §46.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);

(iii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

(A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

(B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

NOTE: *For the continuing review implementation delay period from July 19,2018 through January 20, 2019, institutions may elect to implement certain "burden-reducing" provisions if they plan to transition their research to comply with the 2018 HHS requirements ("Revised Common Rule"). One of these provisions is the allowance for no annual continuing review of certain categories of research.*

NOTE: *Per §46.115, the IRB/EC or CRS must document the IRB/EC's transition decision (including the date of the decision). CRSs must keep this documentation in their regulatory binder at the site.*

In the above instance, if the site's reviewing IRB/EC elects to implement the burden-reducing provision and determines that a study does not require continuing review under the 2018 HHS continuing review requirements at §46.109(f))(1) and will not conduct continuing reviews annually during the delay period, sites must submit to the DAIDS PRO documentation from the IRB/EC that documents this IRB/EC determination, including reference to the applicable CFR that states the reason an annual continuing review is not required.

If an individual IRB/EC determines that a protocol meets the requirements within §46.109(f) and will not conduct continuing reviews annually, sites must submit documentation from the IRB/EC that documents the determination including reference to the applicable CFR that states the reason an annual review is not required.

For protocols that must undergo continuing review on an annual or more frequent basis, continuing review must be performed prior to the expiration date specified on the IRB/EC approval letter(s) and/or site-specific ICFs. The frequency of ongoing reviews should be documented in IRB/EC policies and procedures and may be protocol/study specific. CRSs can visit the OHRP website for additional guidance related to continuing review.

CRSs participating in NIAID (DAIDS)-supported and/or -sponsored clinical trials, reviewed by the DAIDS Scientific Review Committees and are protocol registered are required to submit documentation of IRB/EC Continuing/Annual review approval to the DAIDS PRO. Continuing/Annual review documentation must be submitted to the DAIDS PRO within 14 days of the CRS receiving final written documentation of IRB/EC Continuing/Annual review approval. The IRB/EC approval of continuing review must be a final approval and not require any modifications or further input by the CRS.

The following documents must be submitted to the DAIDS PRO for all continuing/annual review submissions:

- A copy of the IRB/EC Continuing/Annual review approval/determination letter AND any other appropriate documentation from the IRB/EC. *(Refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual.)*

- A copy of the IRB/EC approved site-specific ICF(s) if revised at the time of Continuing/Annual review.

- A copy of the CRS's IRB/EC and other applicable RE/Regulatory Authority(ies) submission letter(s).

- A copy of all correspondence between the CRS and IRB/EC and other applicable RE/Regulatory Authority(ies).

NOTE: *All IRB/EC approval letters for Continuing/Annual review must state that the approval is for continuing review (i.e., similar terminology is acceptable: yearly review, annual review)*

NOTE: *Documentation of IRB/EC receipt of continuing review request alone does not satisfy the DHHS requirement regarding documentation of Continuing/Annual review and approval by the IRB/EC.*

NOTE: *The DAIDS PRO will not review any revised site-specific ICF(s) submitted with the continuing/annual review registration submission.*

CRSs will only be sent a Confirmation of Submission notice that indicates continuing/annual review materials have been received by the DAIDS PRO. CRSs will *NOT* receive any additional notifications from the DAIDS PRO for Continuing/Annual review documentation unless there is a problem with the documentation submitted (i.e., incomplete packet or inappropriate review by the IRB/EC). If problems are noted, the DAIDs PRO will follow-up via e-mail to inform the CRS about the deficiencies and to request corrected continuing/annual review documentation.

If a CRS's IRB/EC procedures for expedited review deviate from those as specified in OHRP guidance (i.e., specific pre-approved country procedures), then the CRS must provide documentation of the IRB/EC procedures to the DAIDS PRO at the same time the CRS submits their IRB/EC Continuing/Annual review approval documents. In addition, documentation of any change in timing of the IRB/EC review procedure for Continuing/Annual reviews for the CRS must be submitted to the DAIDS PRO along with the final IRB/EC Continuing/Annual review approval letter(s).

Lapses in Continuing Review

Per the DHHS regulations 45 CFR 46.103(b) and 46.109(e) and OHRP guidance on continuing review, if there is a lapse in continuing review (i.e., If an investigator has failed to provide continuing review information to their IRB/EC or the IRB/EC has not reviewed and approved a research study by the Continuing/Annual review date specified by the IRB/EC), the research at the CRS must stop, unless the IRB/EC finds that it is in the best interest of individual participants to continue participating in the research interventions or interaction. Enrollment of new participants cannot occur after the expiration of IRB/EC approval(s).

CRSs should contact their DAIDS Office for Clinical Site Oversite (OCSO) representative and/or DAIDS Program Officer when there is any lapse and for additional guidance and information.

CRSs should submit IRB/EC lapse documentation (i.e., the site's documentation of the lapse to the IRB/EC and the IRB/EC's response) to the DAIDS PRO.

7. Site Initiated Revisions to Site Informed Consent Forms (ICFs)

Modifications to a CRS's site-specific ICFs are considered site initiated when the changes are made as a result of new information or at the request of the IRB/EC and other applicable REs/ Regulatory Authority(ies).

Revisions to a CRS's site-specific ICFs are only considered site-initiated when revisions have been made after the CRS has received a Registration Notification from the DAIDS PRO for the most current DAIDS-approved protocol version. Any changes made to a CRS's ICF(s) prior to receiving a Registration Notification from the DAIDS will be considered part of the CRS's initial or amendment registration. For additional information on initial and amendment registration submissions refer to Initial Registration and Amendment Registrations of this manual.

Site-initiated revisions DO NOT affect the final DAIDS protocol version number and CRSs must be sure that the correct DAIDS protocol version number, remains on all site ICF(s). For version tracking purposes at the CRS, CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the final DAIDS protocol version number and/or final version date of the protocol document approved by DAIDS should remain on all site- specific ICFs as well.

The following documentation must be submitted to the DAIDS PRO for all site-initiated revised ICFs:

- A copy of the site-initiated revised ICF(s).
- A copy of the site's IRB/EC and other applicable RE/Regulatory Authority(ies) approval letter(s) and any other appropriate documentation from the IRB/EC other RE/Regulatory Authority(ies). *Refer to Documentation of Institutional Review Board/ Ethics Committee (IRB/EC) and Other Regulatory Entity (RE)/Regulatory Authority(ies) Approvals" of this manual for detailed information)*

NOTE: *If a site initiated revised ICF submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IOR) and/or additional personnel listed in the DPRS will be sent a Requested Materials notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to Requested Materials" of this manual.*

Once the CRS receives approval from their IRB/EC and other applicable RE/ Regulatory Authority(ies), the CRS may implement the revised site-specific ICFs immediately (i.e. without delay, usually at the participant's next scheduled study visit). The DAIDS PRO will not review the site-initiated revisions to CRS's ICFs.

CRSs will be sent a Confirmation of Submission notice that indicates materials have been received by the DAIDS PRO. CRSs will NOT receive any additional notifications from the DAIDS PRO for site-initiated revisions to site-specific ICFs.

8. Updated Form FDA 1572 or DAIDS IOR Form

When there is **any** major change to the information listed on the Form FDA 1572/DAIDS IOR Form submitted to the DAIDS PRO, a CRS should submit an updated Form FDA 1572 (IND studies) or DAIDS IOR Form (Non-IND studies) to the DAIDS PRO within 15 calendar days.

The following documentation should be submitted to the DAIDS PRO for all Updated Form FDA 1572s/DAIDS IOR Forms -

- A copy of the updated Form FDA 1572 signed and dated by the IOR (for studies conducted under an IND), or
- A copy of the updated DAIDS IOR Form signed and dated by the IOR (for non- IND studies).

NOTE: *If there is a Change of IOR (listed in Section 1 of either form), refer to Change of Investigator of Record (IOR)" of this manual.*

NOTE: *CRSs should submit a copy of the signed and dated Form FDA 1572/DAIDS IOR Form to the DAIDS PRO and retain the original version in their regulatory files at the site.*

CRSs will be sent a Confirmation of Submission notice that indicates materials have been received by the DAIDS PRO. CRSs will NOT receive any additional notifications from the DAIDS PRO for updated Form FDA 1572s or DAIDS IOR Form unless the updated document(s) results in a Change of IOR at the CRS.

9. Deregistration

Any CRS that has completed the DAIDS protocol registration process for a protocol (main or sub-study), must complete the DAIDS deregistration process for each protocol to which it is registered.

NOTE: *Deregistration is NOT automatic when a study is completed.*

Deregistration can occur when:

- The CRS no longer has participants on study (all follow-up has been completed) and does not plan to enroll additional subjects.
- If no participants were ever enrolled at the CRS and the study has closed to accrual.

In addition, a CRS should check with their DAIDS Clinical Trials Network or DAIDS Program Officer to confirm if there are any protocol, network and/or DAIDS specific requirements prior to deregistering with the DAIDS PRO and/or closing/terminating the study with the IRB/EC.

The DAIDS deregistration process is independent of a CRS's closure/termination of a study at their IRB/EC. The IRB/EC's determination to close or terminate a study is *NOT* required for a CRS to deregister with DAIDS. Completion of the DAIDS deregistration process indicates that a CRS's participation in a study is complete but does not reflect the closure of a multi-center study at all CRSs participating in the study.

If a CRS plans to complete the DAIDS deregistration process for a study but will not be closing/terminating the study at their IRB/EC, the CRS should consult its IRB/EC to confirm any requirements and/or standard operating procedures that must be met prior to deregistration. A CRS's IRB/EC may require the continued submission of safety information and/or other data for the study. In this case, deregistration with DAIDS PRO should *NOT* be done until the study has been completed at all participating sites.

The following documentation must be submitted to the DAIDS PRO for all deregistration requests:

- Request stating that the CRS no longer intends to participate in the protocol(s), and/or
- A Copy of the IRB/EC closure/termination letter for the protocol if the protocol has been closed with the IRB/EC at the time of deregistration

A CRS will receive a Deregistration Notification from the DAIDS PRO when deregistration has been reviewed and approved by the DAIDS PRO.

NOTE: *A CRS is not considered deregistered until a Deregistration Notification has been issued by the DAIDS PRO.*

Once a CRS receives a Deregistration Notification for a protocol, the CRS is no longer required to submit any additional protocol registration documents to the DAIDS PRO if the protocol amends. A CRS must continue to follow their IRB/EC requirements for submission of documents if the protocol has not been closed/terminated with the IRB/EC.

Upon completion of the DAIDS deregistration process, a CRS will no longer receive safety information (i.e., safety reports, safety memos, investigator's brochures) from the DAIDS RSC Safety Information Center.

Additional guidance is available regarding the DAIDS registration process along with a summary of site responsibilities once deregistration is complete. This information is located on the DAIDS Deregistration Process Guidance under the "Protocol Registration" section.

VII. Definitions

Clinical Research - Research conducted on participants, material, or data of human origin with an identifiable person as the source. Clinical research includes exploratory, behavioral and observational studies. All clinical trials are a subset of clinical research. (DAIDS)

Clinical Research Site (CRS) - Distinct locations (i.e., hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) supported and/or sponsored by NIAID (DAIDS) where qualified professionals conduct clinical research in accordance with good clinical practice (GCP) and applicable regulations. (DAIDS)

Clinical Research Site (CRS) Leader - The onsite senior research scientist responsible for the administrative and scientific components of the CRS. The CRS leader is responsible for overall site activities, including day-to-day operations, performance, and compliance at the site level. (DAIDS)

Clinical Sciences Review Committee (CSRC) - The Division of AIDS internal scientific review committee responsible for the programmatic review of therapeutic protocols sponsored by DAIDS. The review will include careful assessment of the scientific objectives, design, safety, ethics, and feasibility of proposed research protocols. Scientific representatives from collaborating NIH Institutes and Centers participate as appropriate. (DAIDS)

Clinical Trial - A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. (NIAID).

Clinical Trial Applications (CTA): An Investigational New Drug Application for any Product filed with the FDA pursuant to Title 21 of the Code of Federal Regulations, Part 312 ("IND") or the submission to a competent Regulatory Authority within the EU of a request for an authorization concerning a clinical trial, as envisaged in Article 9, paragraph 2, of Directive 2001/20/EC, or any comparable filing made with a Regulatory Authority in another country or territory other than the U.S. or the EU.

Code of Federal Regulations (CFR) - Published by the U.S. Office of the Federal Register National Archives and Records Administration, these are detailed procedures for meeting requirements authorized by law:

> ***Title 21*** - Food and Drugs (covers regulations administered by FDA as authorized by the Food, Drug and Cosmetic Act).
>
> ***Title 45*** - Public Welfare (includes regulations administered by Office for Human Research Protections (OHRP) relating to the protection of human subjects). (DAIDS)

Curriculum Vitae (CV) - A statement of investigator's qualifications including professional experience accomplishments, educational background, and any publications. This document is required for all initial protocol registrations. (DAIDS)

Division of AIDS (DAIDS) - One of six divisions within the National Institute of Allergy and Infectious Diseases. DAIDS is responsible for the initiation, management, and oversight for the clinical trials and research that is sponsored and/or supported by NIAID (DAIDS). (DAIDS)

DAIDS Protocol Registration Office (PRO) - An office within the DAIDS Regulatory Support Contract (RSC) that receives and processes all protocol registration materials for DAIDS. (DAIDS)

DAIDS Protocol Registration System (DPRS) -An internet-based system that allows DAIDS Clinical Research Sites (CRS) to submit and track all documents submitted to the DAIDS Protocol Registration Office (PRO). (DAIDS)

DAIDS Regulatory Support Contract (RSC) - A contract that provides clinical, regulatory and technical support services for NIAID (DAIDS)-supported and/or - sponsored clinical trials. (DAIDS)

DAIDS-sponsored - DAIDS is responsible for the management (including submission of the Investigational New Drug Application (IND) and Investigational Device Exemption (IDE) Application to FDA, and initiation of the study) and oversight for the trial. (DAIDS)

DAIDS-supported - Clinical research activities would be considered to be supported by NIAID (DAIDS) under one or more of the following circumstances:

1. DAIDS provides direct funding to an institution via a grant, contract or cooperative agreement for the clinical research activities; or indirect funding via a subcontract executed under a DAIDS-supported award to another institution.

2. DAIDS provides other tangible support for the clinical research activities which includes, but is not limited to, regulatory support, site monitoring services, study product supply, management and distribution services.

3. DAIDS-supported central laboratory or data management center receives from other organizations specimens or data for processing or analysis and the results or analyses, will be used to direct involvement of participants in clinical research activities. (DAIDS)

Electronic Protocol Registration (EPR) - An alternate way CRSs can submit registration materials via e-mail to the DAIDS PRO if they encounter problems when trying to submit registration materials through the DPRS. (DAIDS)

European Medicines Agency (EMA) - A decentralized agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.

Food and Drug Administration (FDA) - A public health agency within the United States (U.S.) Department of Health and Human Services. FDA's mission is to promote and protect public health by helping safe and effective products reach the market in a timely way and monitoring products for continued safety after they are in use as authorized by The Federal Food, Drug and Cosmetic Act. (DAIDS)

Form FDA 1572 - FDA required document in which clinical investigators agree to conduct the clinical trials according to U.S. federal regulations. The Form FDA 1572 is signed, and a copy submitted to the IND sponsor. (DAIDS)

Full Version Protocol Amendment - Protocol modifications that result in a change in protocol version number. This new protocol version incorporates any currently proposed changes in addition to those made in all Clarification Memos (CMs) and Letter of Amendments (LOAs) that have been approved since the finalization of the previous protocol version. (DAIDS)

International Conference on Harmonisation (ICH) Guidelines
Developed, through a collaboration between the FDA and regulatory agencies in Japan and the European Union, to "harmonize" regulatory requirements to produce marketing applications acceptable to the United States, Japan, and the countries of the European Union. (DAIDS)

Institutional Biosafety Committee (IBC) - Committee set up by an institution under NIH guidelines to review recombinant DNA research and ensure its appropriate use. IBCs may also review other bio hazardous research, including select agents. (NIAID)

Institutional Review Board/Ethics Committee (IRB/EC) - Committee used by an institution to ensure the protection of human subjects by independently approving, modifying, or disapproving research protocols. (NIAID)

Investigational New Drug (IND) Application - A request for authorization from the FDA to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application. (FDA) An IND application is required by the FDA before clinical trials of an investigational drug or biological agent may be initiated. An IND is also generally required if the U.S. FDA has not approved the route of administration, dosage level, or patient population for the drug or biological agent. (DAIDS)

Investigator of Record (IOR) - The individual at the CRS responsible for ensuring that a clinical trial is conducted in accordance with the protocol, applicable U.S. federal regulations, in-country regulations and any provisions imposed by the reviewing IRB/EC/other regulatory entity. This person is the signatory for the Form FDA 1572 for studies conducted under an IND or the DAIDS Investigator of Record Form for non-IND studies.

Investigator of Record (IOR) Form - A document required by DAIDS for non-IND studies. By signing the document, the IOR accepts full responsibility for conduct of the trial at their CRS. (DAIDS)

Letter of Amendment (LOA) - A revision to a protocol made by the Protocol Team/Chair/Awardee through a letter that requires DAIDS final approval/sign-off before implementation. Changes described in a LOA are listed in a document that is separate from the protocol document itself and will NOT result in the change to the DAIDS protocol version number. (DAIDS)

National Institute of Allergy and Infectious Diseases (NIAID) - NIH institute that conducts and supports research to understand, treat, and prevent infectious, immunologic, and allergic diseases. (NIAID)

National Institutes of Health (NIH) - A Federal agency whose mission is to improve the health of the people of the United States. NIH is a part of the Public Health Service, which is part of the U.S. Department of Health and Human Services. (NIH)

Observational Study - A type of study in which individuals are observed or certain outcomes are measured, but no treatments or interventions are assigned by the study. (DAIDS)

Office for Human Research Protections (OHRP) - U.S. Department of Health and Human Services (DHHS) office overseeing human subject protection regulations for HHS-supported research. (NIH)

Office for Policy in Clinical Research Operations (OPCRO) - An office in DAIDS that provides a variety of clinical research management resources and oversight to the DAIDS clinical research portfolio. This includes overseeing the development, standardization, implementation and execution of policies, procedures and standards of conduct for all DAIDS domestic and international clinical research. (DAIDS)

Prevention Sciences Review Committee (PSRC) - The Division of AIDS internal scientific review committee responsible for the programmatic review of vaccine and prevention protocols sponsored by DAIDS. The review will include careful assessment of the scientific objectives, design, safety, ethics, and feasibility of proposed research protocols. Scientific representatives from collaborating NIH Institutes and Centers participate as appropriate. (DAIDS)

Protocol Registration Notifications - The following are notifications that a CRS may receive from the DAIDS PRO:

1. ***Confirmation of Submission*** - A notification sent out to the CRS Coordinator and IOR confirming that registration materials have been successfully submitted to the DAIDS PRO. If a CRS does not receive a Confirmation of Submission Notification within 24-48 hours of submitting registration documents to the DAIDS PRO, the CRS should contact the DAIDSPRO to find out how to proceed.

2. ***Registration Notification*** - A final notification from the DAIDS PRO indicating that a CRS has successfully completed the protocol registration process.

3. ***Registration with Required Corrections Notification*** -A notification from the DAIDS PRO indicating that a CRS must make required corrections and submit them to their IRB/EC for review and approval OR must submit justification for why the required correction will not be made within 120 calendar days of the date the Registration with Required Corrections Notification was issued. A Registration with Required Corrections Notification indicates that a CRS may begin using the site- specific informed consent forms (ICFs) after protocol activation by the appropriate Operations Center, Data Management/Statistical Center or DAIDS Program.

4. ***Disapproval Notification*** - A notification from the DAIDS PRO indicating that the site-specific informed consent forms (ICFs) do not include all the required basic and additional elements to comply with U.S. federal regulations and DAIDS policy. The Disapproval Notification will outline the deficiencies that must be revised/corrected before a final Registration Notification can be issued. All revised site-specific ICFs must be approved by the IRB/EC prior to submission to the DAIDS PRO. A disapproval notification is NOT a final notification since corrective materials must be resubmitted.

5. ***Deregistration Notification*** - A final notification from the DAIDS PRO indicating that a CRS is no longer registered to a study and all associated sub-studies.

6. ***Change of IOR Approval Notification*** - A final notification from the DAIDS PRO indicating that DAIDS has approved the change of IOR for a protocol at a CRS.

7. ***Requested Materials Notice*** - A message from the DAIDS PRO indicating that additional/corrected materials are required as a result of an incomplete or inaccurate submission to the DAIDS PRO.

A Materials Request Notification stops the registration review process until the requested materials have been received at the DAIDS PRO. (DAIDS)

Protocol Registration Team (PRT) - A team within OPCRO responsible for managing the Protocol Registration (PR) process, which includes oversight of the DAIDS PRO. (DAIDS)

Regulatory Entity (RE)/Regulatory Authority - Any entity/body that has the power to regulate which includes authorities that review submitted clinical data and those that conduct inspections. These are sometimes referred to as competent authorities. These are entities/bodies whose approval/authorization/acknowledgment of a clinical trial is required for conducting a clinical trial. Any organization whose approval is required prior to a CRS's participation in DAIDS funded and/or Sponsored Clinical Trial. Includes but not limited to approvals from state/national health systems and administrative bodies, drug agencies etc. (DAIDS adopted from ICH E6)

Sub-Investigator - Any member of the clinical research team designated and supervised by the CRS Leader/IOR of a protocol at a CRS to perform critical trial related procedures and/or to make important clinical trial-related decisions. (DAIDS)

Sub-Study - A sub-study asks a separate research question from the parent protocol and may or may not contribute to the parent protocol's objectives but uses all or a subset of study participants or specimens. A sub-study can be included as part of the main/parent protocol document or may not be included in the main protocol but requires current or previous participation in the main protocol. (NIAID)

The following are different types of sub-studies that a site may protocol register:

1. ***Embedded Sub-study*** - A sub-study that is part of a main protocol that may or may not have a separate ICF. Embedded sub-studies have the same protocol version number as the main study and have a separate protocol number and/or DAIDS protocol ID number. If there is a full version Amendment to the main study, when protocol registering to the amendment, sites are required to protocol register to all embedded sub-studies. A CRS will receive a registration notification for each embedded sub-study that is submitted for protocol registration. LOA registrations are only completed under the Main study however if the LOA requires revision to the sub-study IC, then the site IC should be submitted under the sub-study as a Site Revised IC.

2. ***Stand Alone Sub-study*** - A sub-study that is not part of the main protocol but requires participants to be enrolled in the main study or have previously participated in the main study. A stand-alone sub-study is an independent protocol that may or may not have the same protocol version number/date as the main study and will always have a separate protocol number and/or DAIDS protocol ID number. A CRS should submit all required documents (i.e. IRB/EC approval letter[s], site-specific informed consent form[s], Form FDA 1572 and/or DAIDS IOR Form, and IOR CV) when registering to a stand- alone sub-study. A CRS will receive a registration notification for each stand-alone sub-study that is submitted for protocol registration. (DAIDS). Amendment and LOA registrations should be submitted independently from the main study.

VIII. DAIDS Protocol Registration Office Contact Information and DPRS Access

The DAIDS Protocol Registration Office (PRO) has two different e-mail addresses - one for submission of protocol registration documents and a second for questions and general correspondence.

A. Contact Information for Questions and General Correspondence

E-mail: protocol@tech-res.com
Phone: 301-897-1707
Office Hours: Monday through Friday 8:30 AM to 5:00 PM (U.S. Eastern Standard Time)

Effective January 2012, all sites participating in NIAID (DAIDS)-supported and/or - sponsored clinical research that requires protocol registration, are required to submit protocol registration materials to the DAIDS PRO through the DAIDS Protocol Registration System (DPRS). Information on the DPRS and how to access the system is available on the DPRS website or information on how to submit protocol registration materials through the DPRS once a CRS has received a user name and password, refer to Appendix A of this manual.

In order to gain access to the DPRS, site personnel must complete the DPRS training that's available online at DAIDS Learning Portal.

First, log in to the DAIDS Learning Management System (LMS) with your user name and password. Then enter DPRS into the search field and select the DPRS training course. If you do not have a DAIDS LMS account, click to request account access.

At the time of completion of the DPRS training, a username and password will be provided to the person who completed the training. If DPRS login details have not been received, contact DAIDS-ES Support at CRMSSupport@niaid.nih.gov.

If a CRS encounters problem when submitting protocol registration materials through the DPRS, a CRS can submit protocol registration materials via e-mail to the DAIDS Electronic Protocol Registration (EPR) mailbox. If a CRS submits materials through the EPR mailbox, the e-mail message must outline the details of what is being submitted, and the kind of registration that is being submitted.

Information on protocol registration timelines is available on the DAIDS RSC Website under the "Protocol Registration" section.

B. Appendix A - Instructions on How to Access and Submit Protocol Registration Materials through the DAIDS Protocol Registration System (DPRS)

How do I gain access to DPRS?

1. DPRS Access

DPRS can be accessed via the DAIDS Learning Portal. DPRS Training completion is required to gain DPRS access. Log into the DAIDS Learning Management System (LMS) with your user name and password. Then enter DPRS into the search field and select the DPRS training course. If you do not have a DAIDS LMS account, click here to request account access.

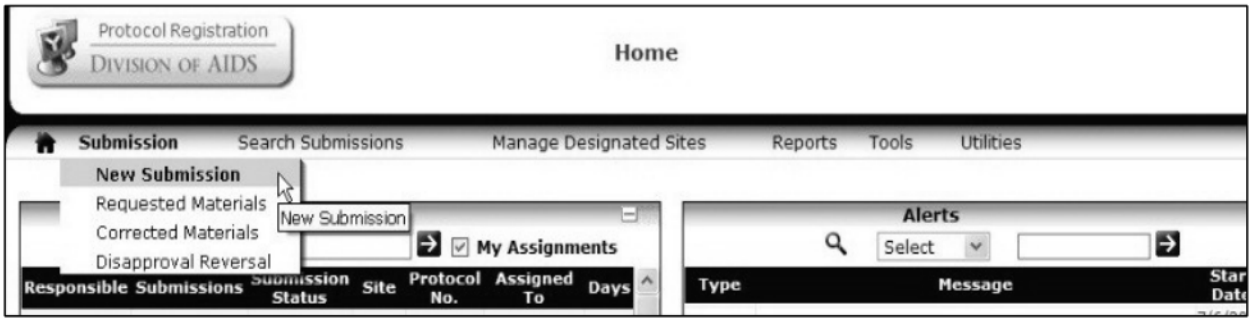
Once the DPRS training has been completed, DPRS user log-in and password will be sent to the trainee. If the training has been completed, but have not received DPRS login details yet, contact DAIDS-ES Support at CRMSSupport@niaid.nih.gov.

2. How do I access the New Submission screen?

Go to the DAIDS Protocol Registration Page. Enter your user name and password and click **Login**.

From the Home Page, click Submission on the main navigation bar and then click New Submission from the drop-down menu, which takes you to the New Submission page.

Figure 1: New Submission Option



3. How do I complete the Site Submission process?

Enter the Submission Details - Enter the appropriate information under the **Site and Protocol details** heading. Click the LOV icon to select the Site, IOR and Protocol No. Click the list of values to select the version/LOA.

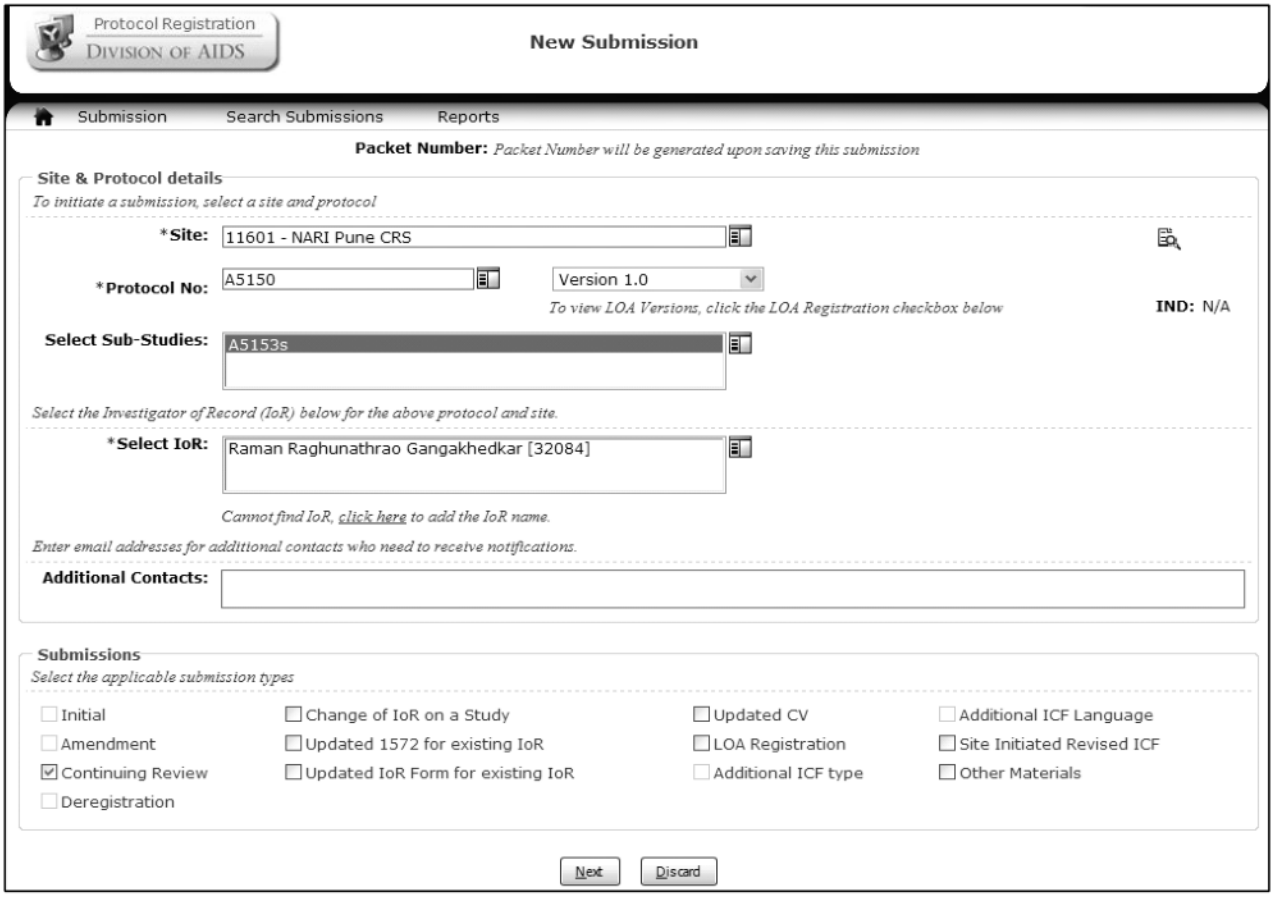
Select Sub-Studies - This list of values displays all embedded sub-studies associated with the study. Select a sub-study displayed to submit materials for the sub-study along with the study. The packet will be created when the main study is submitted.

Submissions - Select the appropriate checkboxes under the Submissions heading.

NOTE: *The system selects the same submission type for the sub-study as on the main study.*

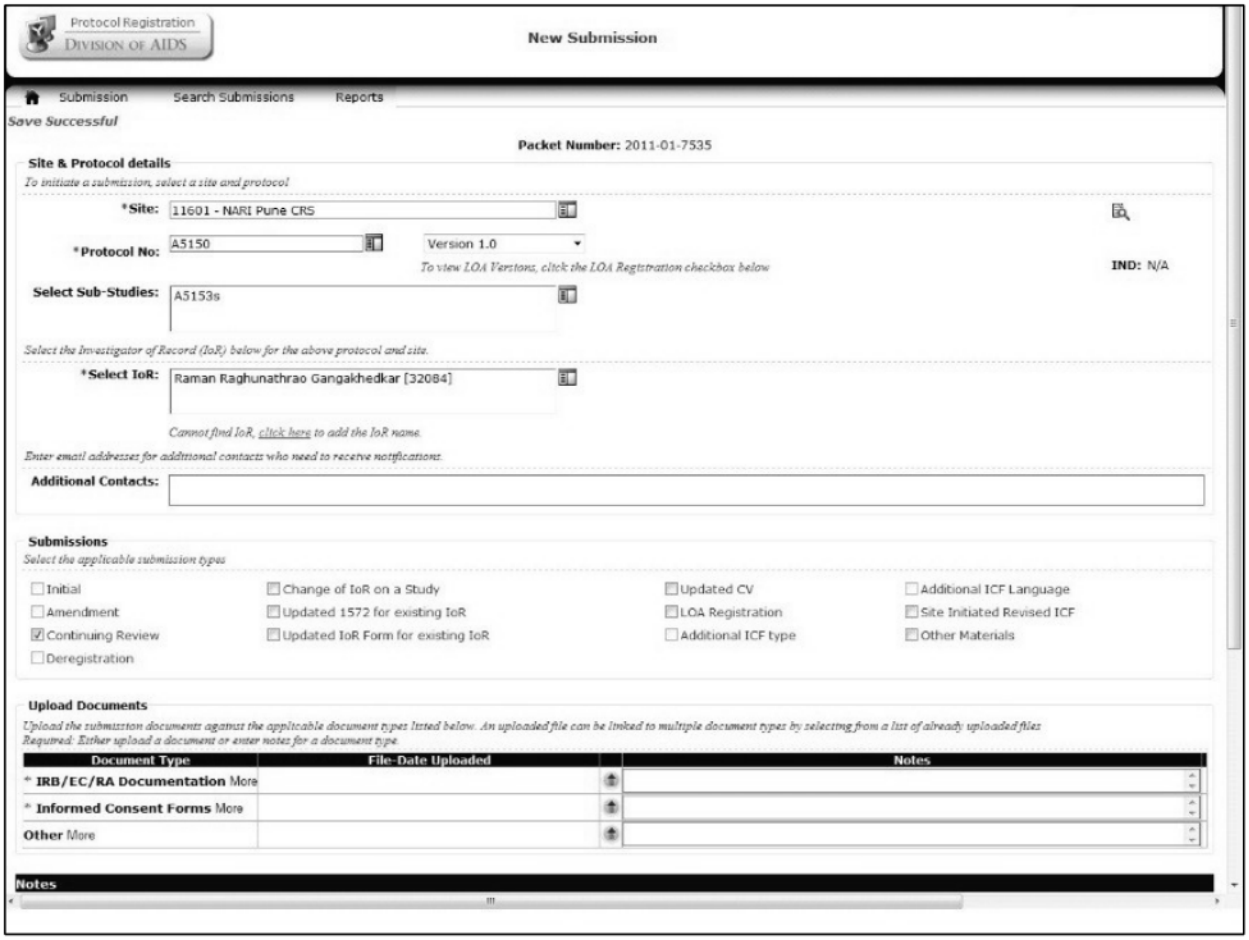
Next - Click **Next**. If the save is successful, the Upload Documents heading appears in the lower half of the screen.

Figure 2: Enter details in the New Submission screen.



Upload Documents - Click the upload icon to upload the appropriate documents. Enter notes to provide additional clarification. Click **Save**.

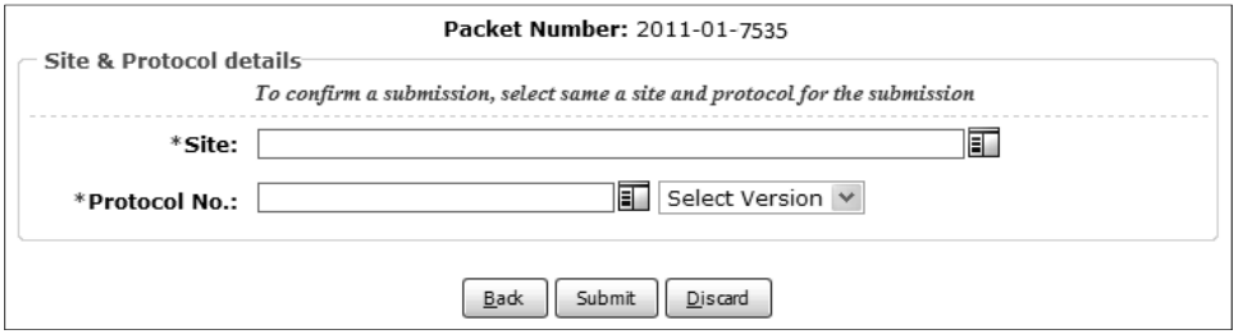
Figure 3: Upload documents in the New Submission screen and add notes.



Confirm Submission Details - When finished, click **Submit**. At the pop-up confirmation window, confirm the Site, IOR Name and Protocol No. Select the version and again click **Submit**.

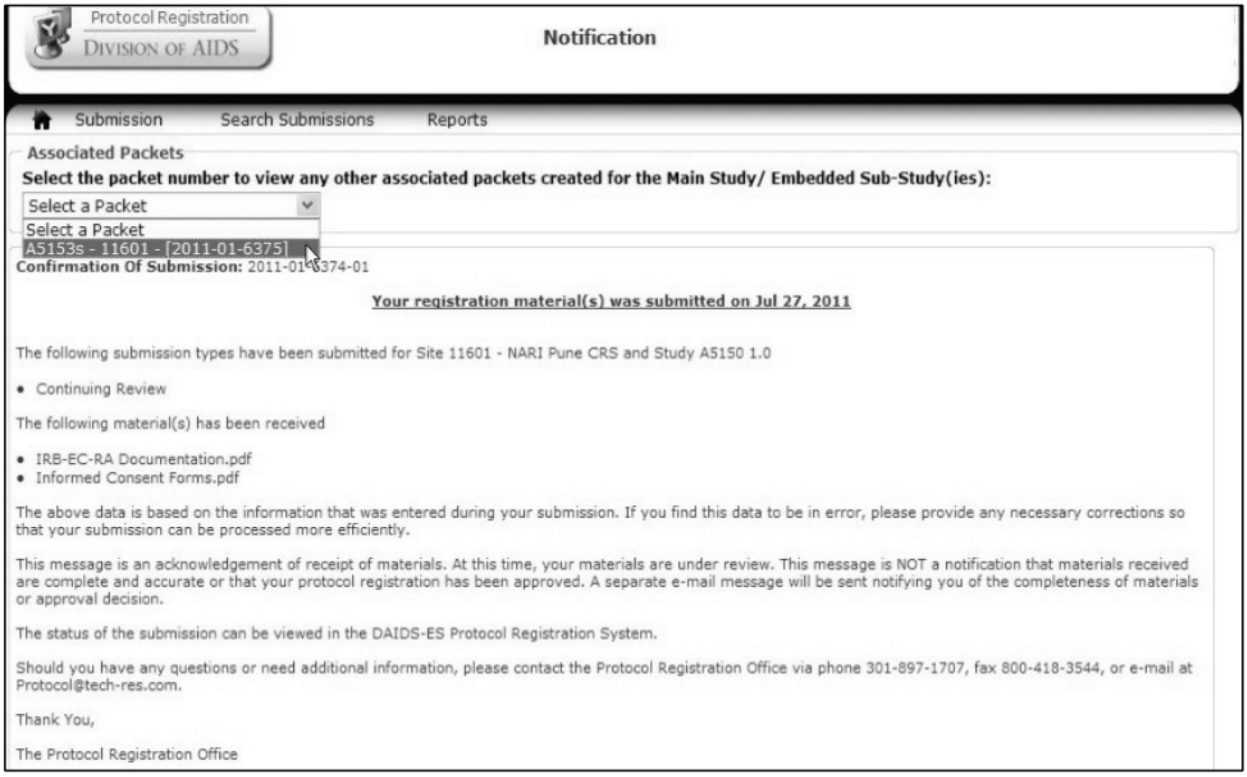
The system confirms whether the submission was successful.

Figure 4: Confirm Submission Details.



Optional - System will provide option to submit sub-study packets that have not yet been submitted by selecting a packet number at the top of the Notification screen.

Figure 5: Navigate to associated packets yet to be submitted.



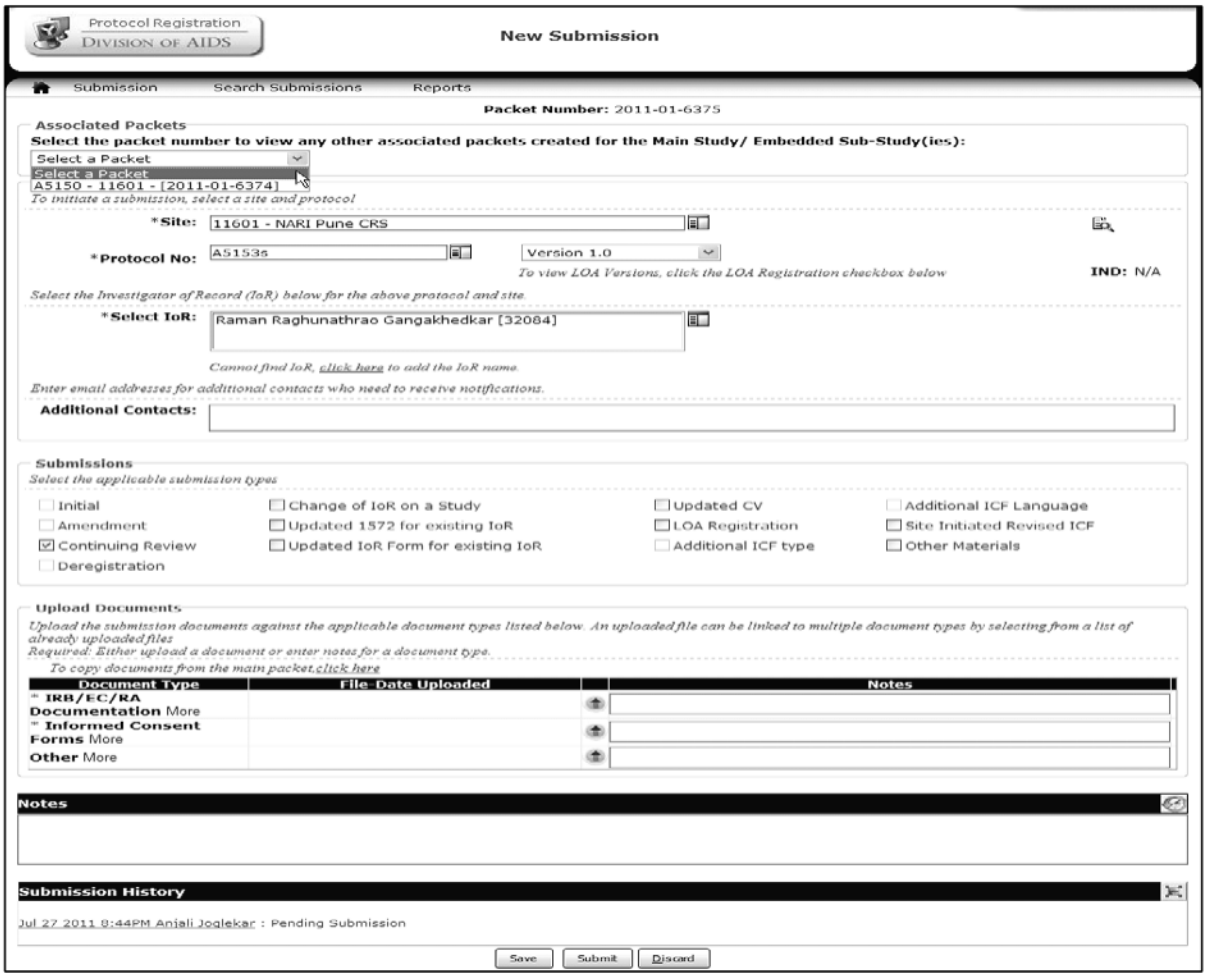
4. How do I view the sub-study packet?

Select a packet number at the top of the screen to view any other associated packets for this study. The Sub-Study screen appears similar to the main submission except the Protocol Number is changed to the sub-study number. The submission type remains the same.

NOTE: *You can use this feature to toggle between the sub-study packets. You also can copy person information to sub- study packets.*

Click the Upload Documents hyperlink in the associated packets to copy documents from the main packet.

Figure 6: Viewing the sub-study packet.



5. Still Have Questions?

E-mail: CRMSSupport@niaid.nih.gov

Phone: 1-240-778-2517

IX. DAIDS Protocol Registration Revision History and Approval

MAN-A15-OPC-001.00 is the initial version of the DAIDS Protocol Registration manual submitted to the DAIDS Quality Management System (QMS) as version 00. Refer to section II. for a detailed list of updates for this version.

There were four previous versions of the DAIDS Protocol Registration Manual, August 2004, March 2010, May 2012, and April 2015 published on the DAIDS Clinical Research Policies webpage prior to the implementation of the DAIDS QMS in 2018

Printed Name/Title	Signature	Date

1.0 PURPOSE

This document states the requirements for the publication, presentation, and disclosure of any work conducted by the AIDS Clinical Trials Group (ACTG) Network, or governed by subcontract agreements executed by Partners HealthCare (PHS) on behalf of the ACTG.

2.0 SCOPE

This SOP applies to all ACTG-related publications including manuscripts, abstracts, Executive Summaries, Clinical Trials Unit (CTU)/Clinical Research Site (CRS) Scientific and Participant Summaries, and press releases.

It is the policy of the ACTG to publish and share research results in a timely manner in accordance with the NIH Public Access Policy http://publicaccess.nih.gov/policy.htm. It is also the policy of the ACTG to publish the results of the main study/project primary manuscript prior to those of substudies and secondary manuscripts, unless otherwise approved by the Scientific Agenda Steering Committee (SASC). This policy is expected to be followed for ACTG studies, collaborative studies with cosponsoring agencies or other clinical trials networks, and studies in which data are collected and analyzed by a network or group other than the ACTG Statistical and Data Management Center (SDMC), unless alternative policies are mutually agreed upon and codified in the Clinical Trials Agreement (CTA), Letter of Understanding (LOU), or Memorandum of Understanding (MOU), or otherwise approved by the ACTG Executive Committee (AEC).

Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), or the AEC, with DAIDS/NIAID approval, have authority to embargo any/all information in Executive Summaries and accompanying documents, CTU/CRS Scientific Summaries, Participant Summaries, and press releases, until information is made public (i.e., abstract presentation or manuscript publication).

3.0 DEFINITIONS

3.1 **Writing Team**—A subgroup of the protocol team members who collaborate to write an abstract or manuscript summarizing results of the study protocol. Under certain circumstances, specialists who are not protocol team members may be included.

3.2 **Masthead authors**— The group that is listed as authors on the manuscript or abstract.

3.3 **Scientific Committee (SC)** —Committee responsible for reviewing manuscript or abstract prior to journal or conference submission, includes Transformative Scientific Groups (TSGs), Collaborative Science Groups (CSGs) and SASC.

3.4 **Designated committee reviewer**—Committee member assigned to review manuscript or abstract prior to journal or conference submission if Scientific Committee chair and vice chair have conflicts.

3.5 **Primary manuscript**—Manuscript that reports data and results of primary objectives of a trial.

3.6 **Secondary manuscript**—Manuscript that reports secondary analysis results or objectives of a trial, or scientific questions outside the primary objectives, e.g., baseline data reports, secondary objectives specified in the protocol, cross-protocol data, or analysis of specimens collected as part of a trial, but used for analyses not previously specified in the primary protocol.

3.7 **New Work Concept Sheet (NWCS)**—Study that reports results of analysis of specimens from an existing ACTG protocol that is not specified in an ACTG protocol or defined as a secondary analysis within 60 days of receipt of the final analysis by the writing committee chair. (See SOP ACTG-109, NWCS Development and Review)

3.8 **Data Analysis Concept Sheet (DACS)**—Study that reports results of analysis of data from an existing ACTG protocol(s) that were not specified in the ACTG protocol or defined as a secondary analysis for that ACTG protocol within 60 days after receipt of the final analysis by the writing committee chair. (See SOP ACTG-106, DACS Development and Review)

3.9 **Non-Protocol related abstract or manuscript**—An abstract or manuscript that is not affiliated to an ACTG protocol that contains ACTG-related data (e.g. related to committee, site or laboratory, ACTG policies, process, or procedure-related).

3.10 **Abstract**—Brief report of ACTG-related data, prepared for submission to a conference. May be classified as a regular abstract or a late-breaker abstract.

3.11 **Protocol team**—Group of team members that appear in the protocol roster, which usually includes pharmaceutical/industry representatives and other funders of the study.

3.12 **Executive Summary**—Summary of ACTG study results of the primary objectives of a trial; disseminated prior to public presentation or publication of the results.

3.13 **CTU/CRS Scientific Summary**—Limited scientific summary of the study results; disseminated to ACTG CTUs and CRSs prior to public presentation or publication of the results, if a full Executive Summary is not warranted.

3.14 **Participant Summary**—Summary for study participants describing the study results and implications of them. To be distributed with Executive Summary or CTU/CRS Scientific Summary.

3.15 **National Institutes of Health Manuscript Submission System (NIHMS)**—An online system for submitting and managing final, peer-reviewed manuscripts in accordance with the NIH Public Access Policy.

3.16 **PubMed Central (PMC)**—The National Institute of Health (NIH) digital archive of full-text, peer-reviewed journal articles; its content is publicly accessible and integrated with other databases (see: http://www.pubmedcentral.nih.gov/).

3.17 **Publication costs**—The author fees associated with publishing peer-reviewed manuscripts.

3.18 **Primary Completion Date**—The date on which the last participant in a clinical study was examined or received an intervention and that data for the primary outcome measure were collected.

4.0 RESPONSIBILITIES AND PROCEDURES

4.1 ACTG Manuscripts

Primary Manuscripts

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Formation of writing team	~ 15 weeks prior to closed to follow-up date/primary completion date	• Form writing team • Notify ACTG Publications Office and committee leadership of writing team members (see *Appendix 1: Writing Team Guidelines*). • Review writing team membership; if necessary make recommendations	Protocol Core Team Protocol Chair/Writing Chair and/or CTS SC Chair/Committee Leadership
Preparation of data analysis plan	12 weeks prior to closed to follow-up date/primary completion date.	• Define analysis plan prior to initiation of final data analysis. (See SOP ACTG-101) ○ Analyses using non-Statistical and Data Analysis Center (SDAC) statistical expertise must follow SOP ACTG -141 for the procedure for conduct of secondary analyses when SDAC resources are not available.	Writing Team
Determination of summaries	Near finalization of data analysis plan	• Determine a need for Executive Summaries and/or CTU/CRS Scientific Summaries based on primary analysis plan, or a preliminary analysis prior to preparation of full primary analysis report (see table for Executive Summary and/or CTU/CRS Scientific Summaries).	SC Chair, in consultation with DAIDS, SASC, protocol Chair, and statistician
Receipt of final primary analysis by protocol chair	5 months post closed to follow-up date (may be accelerated under select circumstances upon team agreement. SC and SDAC agreement is required in select cases).	• Send final analysis to protocol chair • Notify ACTG Publications Office that analysis has been sent	Protocol statistician Writing Chair, statistician, and/or CTS

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
60-Day preparation of manuscript	Upon receipt of primary analysis	• Oversee timely completion of manuscript and adherence to timelines	Committee Leadership/Writing Chair
		• Ensure that the journal's requirements are read and understood prior to any submission of a manuscript. If there are questions regarding special requirements/situations that are unfamiliar, the writing chair should consult with the ACTG Publications Office prior to submission of the manuscript. Questions regarding author's rights should be directed to the author's institution.	Writing Chair
		• Determine number and order of masthead authors; acknowledge ACTG support in the manuscript. When possible, journals should be chosen that do not limit the number of authors in the masthead. (See *Appendix 1: Writing Team Guidelines and Acknowledgements section*)	Writing Team
		• Contact ACTG Publications Office to solicit names and grant numbers of participating sites	Writing Chair
		• Finalize manuscript within 60 days from date final analysis is received by protocol chair.	Writing Team
30- Day Team Review of manuscript by masthead authors, writing team, and protocol team to include DAIDS, SDAC, and the pharmaceutical and biomedical representatives	Following 60-day writing period	• Send manuscript for 14-day review and sign-off (see *Appendix 3* for 14-day review distribution list). Pharmaceutical and biomedical industry representatives are allowed up to 30 days for review, unless otherwise specified in the CTA[2]. *NOTE: It is the Writing team's responsibility to ensure that all of the pharmaceutical/industry reps have been allowed adequate time to review the manuscript.* • If not already addressed in the Clinical Trials Agreement, request that the pharmaceutical company provide a statement indicating their willingness to share the study's protocol with the public at the journal's request.	Writing Chair

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Completion of final analysis report	Within 90-days after final primary analysis is received	• Send final analysis report with relevant additions to ACTG Network principal investigator (PI)/chair and vice chair, SC chair and vice chair ○ If additional analyses necessary for completion of the final analysis report will delay submission of the manuscript for ACTG review, an extension request should be submitted (see *Appendix 2*)	Protocol statisticians
Submission of manuscript for ACTG review following team review	90 days after final analysis is received by protocol chair	• Submit final draft to ACTG Publications Office, via Submission Central on the ACTG member website https://member.actgnetwork.org/pub/cs/review, after final team review. ○ If submitting to an Open Access journal, notify the ACTG Publications Office for determination of Open Access fee coverage (see Appendix 6 for more information).	Writing Chair
ACTG review of manuscript	10 business days	• Send final draft to SC chair/vice chair/designated committee reviewer for approval/disapproval • Send final draft to additional review parties for review concurrent with committee review (See *Appendix 3* for ACTG Publications Office manuscript review distribution list) [2] • Acquire a list of team members with significant financial interests, or a statement that none of them do, from the ACTG Financial Disclosure Coordinator (FDC). • Review manuscript and submit any comments to ACTG Publications Office[2].	ACTG Publications Office Financial Disclosure Coordinator Additional review parties
Completion of ACTG review	Within 10 business days after final draft is disseminated	• Review manuscript and return manuscript endorsement sheet to ACTG Publications Office (see *Appendix 4* for Committee Reviewer Responsibilities). • Send endorsement response and additional review party comments to corresponding author • Respond to review comments (via options below)	SC Chair/Vice-Chair/designated reviewer ACTG Publications Office Writing Chair

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		○ Approved [and reviewer does not want to see MS again]: proceed with submission to journal ○ Approved and reviewer wants to see manuscript again prior to submission: incorporate comments and send revised manuscript and responses to ACTG Publications Office within 20 days. ○ Disapproved: resubmit revised manuscript to ACTG Publications Office within 60 days for 10 day ACTG Review as indicated above. Note: Substantial changes following ACTG review must be agreed on by authors and SC chair/vice chair/designated committee reviewer. If agreement cannot be reached, refer to the SASC chair for resolution.	
Revision and resubmission of manuscript 60 days after acceptance with revisions or rejection	Within 60 days of rejection following initial ACTG review	• Distribute revised manuscript, review comments, and responses to writing team, masthead authors, and protocol team to include SDAC, DAIDS, and the pharmaceutical representatives for a 2nd team review ○ For NWCS and DACS, please resubmit to the team review parties outlined in Appendix 3. • Resubmit revised manuscript to ACTG Publications Office, via Submission Central on the ACTG member website, for a second ACTG review prior to journal submission. ○ Failure to submit for a 2nd ACTG review within 60 days may result in sanctions, as described in *Appendix 5: Sanctions*. • Send manuscript for 2nd 10-day ACTG review to SC Chair/Vice-Chair/designated reviewer • Respond to 2nd review comments via options listed in "Completion of ACTG Review" section above	Writing Chair Writing Chair ACTG Publications Office Writing Chair
Submission to journal	Within 30 days after ACTG approval	• Ensure authors' disclosure of potential conflicts of interest as required by journal policy.	Writing chair

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		• Prior to signing the journal publication agreement (or similar copyright transfer agreement)- ○ Ensure the publishing agreement allows the paper to be posted to PubMed Central, in accordance with NIH Public Access Policy. ○ Contact the ACTG Publications Office for assistance in retaining author rights for compliance to Public Access Policy. • At the time of journal submission, the journal must be notified that the manuscript was funded wholly or in part by NIH. • If a journal requests a statement about access to data, use the following statement: "Study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group." • If a journal requests at statement about access to data and statistical analysis programs, use the following statement: "Study data and statistical programming code are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group. • Submit journal review updates and decisions to ACTG Publications Office within 10 days after receipt. • Maintain copies of journal review comments (to be made available to SASC or SC upon request).	
Journal acceptance for publication	Following notification of acceptance for publication	• Awardees are responsible for ensuring manuscripts are submitted to the National Institutes of Health Manuscript Submission site (NIHMS) upon acceptance for publication. If the manuscript is being published in a journal that does not deposit final published articles in PubMed Central, the author is responsible for submission. The ACTG Publications Office at the Leadership and Operations Center can be contacted for assistance at ACTGPublications@partners.org or designated the submitter of the manuscript if the author is unable. • Approve the release and PubMed Central formatting of your manuscript when receiving the email notification from NIHMS[3]	Writing Chair or senior author

EVENT	PRIMARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		• If the authors are responsible for publication fees, see *Appendix 6: ACTG Publication Costs.*	
Assignment of scientific contribution credit	Within 30 days after publication	• Obtain an electronic copy of the published manuscript and, if appropriate, assign scientific contribution credit for the annual site and laboratory performance evaluations in accordance with SOP ACTG-126, respectively.	Network Coordinating Center
Referencing ACTG published manuscripts	Following publication of manuscript online or in journal	• When submitting an application, proposal, or report to the NIH, the PubMed Central reference number (PMCID) must be included when citing ACTG papers that arise from NIH-funded research.	ACTG members

Baseline and Secondary Manuscripts

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Formation of the writing team	May vary	• Form writing team • Notify ACTG Publications Office and committee leadership of writing team members (see *Appendix 1: Writing Team Guidelines*). • Review writing team membership; if necessary make recommendations	Protocol Core Team Protocol Chair/Writing Chair and/or CTS SC Chair/Committee Leadership
Preparation of data analysis plan	May vary	• Define analysis plan prior to initiation of final data analysis. (See SOP ACTG-101) ○ Analyses using non-Statistical and Data Analysis Center (SDAC) statistical expertise must follow SOP ACTG-158 for the procedure for conduct of secondary analyses when SDAC resources are not available.	Writing Team
Receipt of final analysis by protocol chair	May vary secondary to assays/texts completion	• Send final analysis to protocol chair • Notify ACTG Publications Office that analysis has been sent	Protocol statistician Writing Chair, statistician, and/or CTS

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
60-Day preparation of manuscript	Upon receipt of baseline or secondary analysis	• Oversee timely completion of manuscript and adherence to timelines	Committee Leadership/Writing Chair
		• Ensure that the journal's requirements are read and understood prior to any submission of a manuscript. If there are questions regarding special requirements/situations that are unfamiliar, the writing chair should consult with the ACTG Publications Office prior to submission of the manuscript. Questions regarding author's rights should be directed to the author's institution.	Writing Chair
		• Determine number and order of masthead authors; acknowledge ACTG support in the manuscript. When possible, journals should be chosen that do not limit the number of authors in the masthead. (See *Appendix 1: Writing Team Guidelines and Acknowledgements section*)	Writing Team
		• Contact ACTG Publications Office to solicit names and grant numbers of participating sites (only for major secondary manuscripts)	Writing Chair
		• Finalize manuscript within 60 days from date final analysis is received by protocol chair.	Writing Team

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
30-day team review of manuscript by masthead authors, writing team, and protocol team to include DAIDS, SDAC, and the pharmaceutical and biomedical representatives	Following 60-day writing period	• Send manuscript for 14-day review and sign-off (see *Appendix 3* for 14-day review distribution list). Pharmaceutical and biomedical industry representatives are allowed up to 30 days for review, unless otherwise specified in the CTA[2]. *NOTE: It is the Writing team's responsibility to ensure that all of the pharmaceutical/industry reps have been allowed adequate time to review the manuscript.* • If not already addressed in the CTA, request that the pharmaceutical company provide a statement indicating their willingness to share the study's protocol with the public at the journal's request.	Writing chair
Completion of final analysis report	Within 90-days after final analysis is received	• Send final analysis report with relevant additions to ACTG Network principal investigator (PI)/chair and vice chair, SC chair and vice chair • If additional analyses necessary for completion of the final analysis report will delay submission of the manuscript for ACTG review, an extension request should be submitted (see *Appendix 2*)	Protocol statisticians
Submission of manuscript for ACTG review following team review	90 days after final analysis is received by protocol chair	• Submit final draft to ACTG Publications Office, via Submission Central on the ACTG member website https://member.actgnetwork.org/pub/cs/review, after final team review. • If submitting to an Open Access journal, notify the ACTG Publications Office for determination of Open Access fee coverage (see Appendix 6 for more information).	Writing Chair
ACTG review of manuscript	10 business days	• Send final draft to SC chair/vice chair/designated committee reviewer for approval/disapproval • Send final draft to additional review parties for review concurrent with committee review (See *Appendix 3* for ACTG Publications Office manuscript review distribution list)[2] • Acquire a list of team members with significant financial interests, or a statement that none of them do, from the ACTG	ACTG Publications Office Financial Disclosure Coordinator

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		Financial Disclosure Coordinator (FDC). • Review manuscript and submit any comments to ACTG Publications Office[2].	 Additional review parties
Completion of ACTG review	Within 10 business days after final draft is disseminated	• Review manuscript and return manuscript endorsement sheet to ACTG Publications Office (see *Appendix 4* for Committee Reviewer Responsibilities). • Send endorsement response and additional review party comments to corresponding author • Respond to review comments (via options below) ○ Approved [and reviewer does not want to see MS again]: proceed with submission to journal ○ Approved and reviewer wants to see manuscript again prior to submission: incorporate comments and send revised manuscript and responses to ACTG Publications Office within 20 days. ○ Disapproved: resubmit revised manuscript* to ACTG Publications Office within 60 days for 10 day ACTG Review as indicated above. Note: Substantial changes following ACTG review must be agreed on by authors and SC chair/vice chair/designated committee reviewer. If agreement cannot be reached, refer to the SASC chair for resolution.	SC Chair/Vice-Chair/designated reviewer ACTG Publications Office Writing Chair
Revision and resubmission of manuscript 60 days after acceptance with revisions or rejection	Within 60 days of rejection following initial ACTG review	• Distribute revised manuscript, review comments, and responses to writing team, masthead authors, and protocol team to include SDAC, DAIDS, and the pharmaceutical representatives for a 2nd team review ○ For NWCS and DACS, please resubmit to the team review parties outlined in Appendix 3.	Writing Chair

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		• Resubmit revised manuscript to ACTG Publications Office, via Submission Central on the ACTG member website, for a second ACTG review prior to journal submission. o Failure to submit for a 2nd ACTG review within 60 days may result in sanctions, as described in *Appendix 5: Sanctions*. • Send manuscript for 2nd 10-day ACTG review to SC Chair/Vice-Chair/designated reviewer • Respond to 2nd review comments via options listed in "Completion of ACTG review" section above	Writing Chair ACTG Publications Office Writing Chair
Submission to journal	Within 30 days after ACTG approval	• Ensure authors' disclosure of potential conflicts of interest as required by journal policy. • Prior to signing the journal publication agreement (or similar copyright transfer agreement)- o Ensure the publishing agreement allows the paper to be posted to PubMed Central, in accordance with NIH Public Access Policy. o Contact the ACTG Publications Office for assistance in retaining author rights for compliance to Public Access Policy. • If a journal requests a statement about access to data, use the following statement: "Study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group. • If a journal requests at statement about access to data and statistical analysis programs, use the following statement: "Study data and statistical programming code are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group. • At the time of journal submission, the journal must be notified that the manuscript was funded wholly or in part by NIH.	Writing Chair

EVENT	BASELINE & SECONDARY MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		• Submit journal review updates and decisions to ACTG Publications Office within 10 days after receipt. • Maintain copies of journal review comments (to be made available to SASC or SC upon request).	
Journal acceptance for publication	Following notification of acceptance for publication	• If the manuscript is being published in a journal that does not deposit final published articles in PubMed Central, submit a request with the final peer reviewed version (e.g. Microsoft Word document), all tables, figures, and supplementary information, and a copy of the signed publication agreement (or similar copyright transfer agreement) to PubMed Central via NIHMS. The ACTG Leadership and Operations Center at ACTGPublications@partners.org can be contacted with questions. The Leadership and Operations Center can submit the manuscript on behalf of the corresponding author as a last resort. • Approve the release and PubMed Central formatting of your manuscript when receiving the email notification from NIHMS.[3] NOTE: If the authors are responsible for publication fees, see *Appendix 6: ACTG Publication Costs.*	Writing Chair or senior author
Assignment of scientific contribution credit	Within 30 days after publication	Obtain an electronic copy of the published manuscript and, if appropriate, assign scientific contribution credit for the annual site and laboratory performance evaluations in accordance with SOP ACTG-126, respectively.	Network Coordinating Center
Referencing ACTG published manuscripts	Following publication of manuscript online or in journal	When submitting an application, proposal, or report to the NIH, the PubMed Central reference number (PMCID) must be included when citing ACTG papers that arise from NIH-funded research.	ACTG members

NWCS/DACS Manuscripts

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
NWCS/DACS request for use of study data for NWCS or DACS Based on availability of data for use by investigators outside the protocol team through the submission and approval of a data request, for DACS and NWCS	One year after publication of primary manuscript and team confirmation of secondary analyses to be completed and published by the team	• Once the study data are openly available for use by investigators outside the protocol team, circulate NWCS and/or DACS as a courtesy to the primary protocol team, and if samples are to be used, ascertain whether or not sufficient samples are available for proposed work.	Protocol/Non-protocol investigators
Receipt of final analysis by protocol chair/lead investigator	May vary	• Send final analysis to protocol chair/lead investigator • Notify ACTG Publications Office that analysis has been sent	Protocol statistician Writing Chair, and/or statistician
60 –day preparation of manuscript	Upon receipt of analysis	• Oversee timely completion of manuscript and adherence to timelines • Determine number and order of masthead authors; acknowledge ACTG support in the manuscript. (See *Appendix 1: Writing Team Guidelines and Acknowledgements section*) • Finalize manuscript within 60 days from date final analysis is received by protocol chair.	Committee Leadership/Writing Chair Writing Team Writing Chair
30-day team review by masthead authors to include SDAC, the protocol chairs and pharmaceutical/biomedical industry representatives of the parent protocols	Following 60-day writing period	• Send manuscript for 14-day review and sign-off (see *Appendix 3* for 14-day review distribution list). Pharmaceutical, biomedical industry, or external collaborators are allowed up to 30 days for review, unless otherwise specified in the CTA[2]. *NOTE: It is the Writing team's responsibility to ensure that all of the pharmaceutical/industry reps have been allowed adequate time to review the manuscript.*	Writing Chair
Completion of final analysis report	Within 90-days after analysis received	• Send final analysis report with relevant additions to ACTG Network principal investigator (PI)/chair and vice chair, SC	Protocol statisticians

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		chair and vice chair ○ If additional analyses necessary for completion of the final analysis report will delay submission of the manuscript for ACTG review, an extension request should be submitted (see *Appendix 2*)	
Submission of manuscript for ACTG review following team review	90 days after final analysis is received by protocol chair	• Submit final draft to ACTG Publications Office, via Submission Central on the ACTG member website https://member.actgnetwork.org/pub/cs/review, after final team review. • If submitting to an Open Access journal, notify the ACTG Publications Office for determination of Open Access fee coverage (see Appendix 6 for more information).	Writing Chair
ACTG review of manuscript	10 business days	• Send final draft to SC chair/vice chair/designated committee reviewer for approval/disapproval • Send final draft to additional review parties for review concurrent with committee review (See *Appendix 3* for ACTG Publications Office manuscript review distribution list) [2] • Acquire a list of team members with significant financial interests, or a statement that none of them do, from the ACTG Financial Disclosure Coordinator (FDC). • Review manuscript and submit any comments to Publications Office[2].	ACTG Publications Office Financial Disclosure Coordinator Additional review parties
Completion of ACTG review	Within 10 business days after final draft is disseminated	• Review manuscript and return manuscript endorsement sheet to Publications Office (see *Appendix 4* for Committee Reviewer Responsibilities). • Send endorsement response and additional review party comments to corresponding author • Respond to review comments (via options below)	SC Chair/Vice-Chair/designated reviewer ACTG Publications Office Writing Chair

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		○ Approved [and reviewer does not want to see MS again]: proceed with submission to journal ○ Approved and reviewer wants to see manuscript again prior to submission: incorporate comments and send revised manuscript and responses to ACTG Publications Office within 20 days. ○ Disapproved: resubmit revised manuscript to ACTG Publications Office within 60 days for 10 day ACTG review as indicated above. Note: Substantial changes following ACTG review must be agreed on by authors and SC chair/vice chair/designated committee reviewer. If agreement cannot be reached, refer to the SASC chair for resolution.	
Revision and resubmission of manuscript 60 days after acceptance with revisions or rejection	Within 60 days of rejection following initial ACTG review	• Distribute revised manuscript, review comments, and responses to writing team, masthead authors, and protocol team to include SDAC, DAIDS, and the pharmaceutical representatives for a 2nd team review ○ For NWCS and DACS, please resubmit to the team review parties outlined in Appendix 3. • Resubmit revised manuscript to ACTG Publications Office, via Submission Central on the ACTG member website, for a second ACTG review prior to journal submission. ○ Failure to submit for a 2nd ACTG Review within 60 days may result in sanctions, as described in *Appendix 5: Sanctions*. • Send manuscript for 2nd 10-day ACTG review to SC Chair/Vice-Chair/designated reviewer • Respond to 2nd review comments via options listed in “Completion of ACTG review” section above	Writing Chair Writing Chair ACTG Publications Office Writing Chair

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Submission to journal	Within 30 days after ACTG approval	• Ensure authors' disclosure of potential conflicts of interest as required by journal policy. • Prior to signing the journal publication agreement (or similar copyright transfer agreement)- ○ Ensure the publishing agreement allows the paper to be posted to PubMed Central, in accordance with NIH Public Access Policy. ○ Contact the ACTG Publications Office for assistance in retaining author rights for compliance to Public Access Policy. • If a journal requests a statement about access to data, use the following statement: "Study data are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group." • If a journal requests at statement about access to data and statistical analysis programs, use the following statement: "Study data and statistical programming code are available upon request from sdac.data@sdac.harvard.edu with the written agreement of the AIDS Clinical Trials Group." • At the time of journal submission, the journal must be notified that the manuscript was funded wholly or in part by NIH. • Submit journal review updates and decisions to ACTG Publications Office within 10 days after receipt. • Maintain copies of journal review comments (to be made available to SASC or SC upon request).	Writing Chair
Journal acceptance for publication	Following notification of acceptance for publication	• If the manuscript is being published in a journal that does not deposit final published articles in PubMed Central, submit a request with the final peer reviewed version (e.g. Microsoft Word document), all tables, figures, and supplementary information, and a copy of the signed publication agreement (or similar copyright transfer agreement) to PubMed Central via NIHMS. The ACTG Leadership and Operations Center at ACTGPublications@partners.org can be contacted with questions. The Leadership and Operations Center can submit	Writing Chair or senior author

EVENT	NWCS/DACS MANUSCRIPT TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		the manuscript on behalf of the corresponding author as a last resort. • Approve the release and PubMed Central formatting of your manuscript when receiving the email notification from NIHMS[3] • If the authors are responsible for publication fees, see *Appendix 6: ACTG Publication Costs.*	
Assignment of scientific contribution credit	Within 30 days after publication	Obtain an electronic copy of the published manuscript and, if appropriate, assign scientific contribution credit for the annual site and laboratory performance evaluations in accordance with SOP ACTG-126, respectively.	Network Coordinating Center
Referencing ACTG published manuscripts	Following publication of manuscript online or in journal	When submitting an application, proposal, or report to the NIH, the PubMed Central reference number (PMCID) must be included when citing ACTG papers that arise from NIH-funded research.	ACTG members

[1] *Timeline modified if study closes prematurely*
[2] *Timelines codified in CTA may supersede timelines set in this SOP.*
[3] *Please refer to http://publicaccess.nih.gov/FAQ.htm for an informative list of frequently asked questions.*

4.2 ACTG Abstracts

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Team review of abstract	Prior to submission for ACTG review	• For main protocol or substudy abstracts, submit a request for team review to the writing team, masthead authors, and the protocol team, to include all current members including SDAC[4], DAIDS[4], the protocol chairs, and the pharmaceutical and biomedical industry representatives[3] (if applicable) o For substudies, the main study team and substudy team must be included • For NWCS and DACS abstracts, submit a request for team review to the masthead authors to include SDAC if SDAC[2] is a co-author, the protocol chair(s) of the parent protocol(s), and	Writing Chair

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
		the pharmaceutical and biomedical industry representatives of the parent protocol(s) The ACTG Publications Office can be contacted for this information.	
Submission of abstract for ACTG review	Preferably at least 5 days and no fewer than 72 hours prior to conference organizer deadline[1]	• Send analyses on which abstract is based to ACTG Network PI/chair and vice chair, SC chair and vice chair. • Submit final abstract to ACTG Publications Office, via Submission Central on the ACTG member website, after final team review. • Send final draft to SC chair/vice chair/designated committee reviewer for approval/disapproval and to additional review parties[2] for comments (see *Appendix 3* for ACTG Publications Office abstract review distribution list).	Statisticians Writing Chair ACTG Publications Office
ACTG review of abstract	72 hours prior to deadline	• Review abstract and complete abstract endorsement sheet sent by ACTG Publications Office (see *Appendix 4* for Committee Reviewer Responsibilities). • Submit signed abstract endorsement sheet, which may include additional comments, to ACTG Publications Office upon completion of review.	SC Chair/Vice Chair/designated committee reviewer
Completion of ACTG review	At least 24 hours prior to conference submission deadline	• Communicate SC endorsement and all comments to corresponding and lead author • Respond to review comments (if approved, proceed with next step)— o If not approved by the SC chair/vice chair/designated committee reviewer, either revise and resubmit for a second ACTG review a minimum of 24 hours prior to the conference submission deadline, withdraw the abstract from the conference (if already submitted), or send an appeal to the SASC/Executive Committee chairs.	ACTG Publications Office Writing Chair
Submission to conference organizer	Within 5 days after ACTG approval	Submit abstract to the ACTG Publications Office at the time of conference submission	Writing Chair

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Notification of abstract disposition	Within 10 days after notification by conference organizer	Provide a copy of the disposition to ACTG Publications Office. *Failure to notify the ACTG Publications Office that an abstract has been accepted may result in actions by the SC leadership.*	Writing Chair
If abstract is accepted and dissemination of summaries is required by the TSG/SC	At least 48 hours prior to release to the general public	See Section 4.3 table for Executive Summaries and/or Section 4.4 table for CTU/CRS Scientific Summaries	ACTG Network Coordinating Center
If abstract is accepted and development of press releases is found to be required	Prior to conference	See Section 4.5 table for Press Releases	Pharmaceutical, biomedical industry representatives, protocol team, or NIAID/DAIDS
If abstract is not accepted: Revision and resubmission of abstract	Preferably at least 5 days and no fewer than 72 hours prior to the conference organizer deadline	Notify the ACTG Publications Office of abstract rejection prior to resubmission to another conference. If major revisions occur, re-review is required, otherwise the endorsement stands. Submit revised abstracts to the ACTG Publications Office, via Submission Central on the ACTG member website, for a second ACTG review prior to submission to another conference. Team review is required prior to resubmission for ACTG review.	Writing Chair
Preparation of conference presentation	Prior to conference	• Acknowledge the ACTG and include the ACTG logo on presentation materials. The ACTG logo can be found on the ACTG member website, under Shared Resources, General ACTG information, About ACTG folder (https://member.actgnetwork.org/cms/folder/6169). • Circulate final/near-final poster and/or slides to protocol team, including pharmaceutical, biomedical industry, or other external collaborators, for review. Posters and/or slides do not need to be submitted to the ACTG Publications Office for ACTG review.	Writing Team Writing Chair
Dissemination of accepted abstracts	At least 1 day prior to conference start date	Send copies of accepted abstracts to all CTU PIs and CRS Leaders	ACTG Publications Office
Presentation of conference paper	Within 2 weeks following the conference	Send an electronic copy of the finalized presentation to ACTG Publications Office to be posted on the ACTG website.	Writing Chair

[1] *If data not available in timeframe, alternative review process may be determined by SC, SASC, and Executive Committee chairs.*
[2] *Timelines codified in CTA may supersede timelines set in this SOP.*

[3]If the company changes its name, merges with or is acquired by another company, a representative of the new company must receive the manuscript. Timelines and requirements for manuscript review may be superseded by Clinical Trials Agreement stipulations.
[4]SDAC statistician responsible for distributing for SDAC review; SDAC responsibility to ensure distribution of analysis reports to ACTG Network PI/Chair and Vice Chair and SC Chair and Vice Chair for both abstracts and manuscripts.) DAIDS protocol member (Medical Officer) responsible for distributing for internal DAIDS review.

4.3 ACTG Executive Summaries

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Decision to prepare Executive Summary	Near finalization of primary analysis plan, or a preliminary analysis prior to preparation of full primary analysis report, upon conference acceptance or upon journal acceptance	Make decision to prepare an Executive Summary	SC leadership, in consultation with DAIDS, protocol Chair, and/or statistician, and SASC
Preparation of Executive Summary and Participant Summary	Within 60 days after the decision to prepare Executive Summary	• Oversee and contribute to the team's drafting of Executive Summary, based on primary analysis report, or a preliminary analysis prior to preparation of full primary analysis report, and Participant Summary. Draft must state that the material is confidential and not for public distribution. • Urgent summary: submit written request to SC chair, and/or SASC and Executive Committee chairs specifying reason for an altered timeline.	Protocol Chair and team statistician, or designated team member Protocol Team

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Protocol team review	Within 30 days after protocol chair receives final primary analysis (for decisions made during preparation of analysis report) or < 14 days before conference presentation/journal publication	• Send Executive Summary and Participant Summary drafts to CTS for distribution to protocol team, and pharmaceutical, biomedical industry, or other external collaborators if not on team log on for 5-day review. Team members may not disseminate results prior to Executive Summary release. • Receive comments from reviewers. Allowed 2-5 days to incorporate team comments into final drafts. (Timeframe contingent on conference presentation date or anticipated journal publication date.)	Protocol Chair and team statistician, or designated team member
Scientific Committee, ACTG Network PI/Chair, SASC, collaborator, and DAIDS review	Following protocol team review and incorporation of team comments	• Forward final drafts to the DAIDS, the relevant SC leadership, the ACTG Network PI/Chair, and the SASC chair for 5-day review. Summaries cannot be disseminated until approval from all parties is received. • In the event of disagreement, work with the review groups to reach agreement. If agreement cannot be reached, appeals should follow the ACTG appeal and grievance procedure (SOP ACTG -120)	ACTG Network Coordinating Center SC Chair
Dissemination of Final Executive Summary, Participant Summary, and accompanying documents	Upon approval by SC, ACTG Network PI/chair, SASC chair, collaborators, and DAIDS and at least 48 hours prior to public release	Electronically distribute Executive Summary, Participant Summary, and accompanying documents (i.e., press release, question and answer documents and note to physicians) with statement indicating information is embargoed until public presentation or publication (see *Appendix 3* for Executive Summary dissemination list).	ACTG Network Coordinating Center

4.4 ACTG CTU/CRS Summaries

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY(IES)
Preparation and review of CTU/CRS Scientific Summary and Participant Summary	If the decision is made that an Executive Summary is not needed and the summaries are required per the SC leadership.	• Prepare Scientific Summary and Participant Summary. • Review and approve the Scientific and Participant Summaries prior to dissemination.	Protocol Team Relevant SC leadership, ACTG Network PI/Chair, SASC chair, DAIDS, pharmaceutical, biomedical industry, or other external collaborators
Dissemination of CTU/CRS Scientific and Participant Summaries	At least 48 hours prior to the first public presentation of the results	Distribute Scientific Summary with Participant Summary to the CTU PI, CRS Leader, and CTU and CRS Coordinators with a statement indicating that the information is embargoed until public presentation or publication.	CTS

4.5 ACTG Press Releases

4.5.1 If prepared for published or presented abstracts reporting preliminary study results prior to completion of final study results, only data from published/presented abstract is normally permitted for use in press release. Additional data may be included with the express permission of the protocol team and the ACTG Network PI/Chair.

4.5.2 Press releases to be issued by the ACTG on behalf of its own studies should be prepared by the protocol team.

4.5.3 The Protocol team, pharmaceutical, biomedical industry, or external collaborators, and NIAID/DAIDS must work directly with the ACTG Communications Manager, actg.communications@fstrf.org, on all press releases.

EVENT	TIMELINE	PROCEDURES	RESPONSIBLE PARTY/PARTIES
Preparation of a press release by pharmaceutical, biomedical industry, or external collaborators*	When study is complete and an abstract is published/presented, but final results and/or primary manuscript are not published or if primary/secondary manuscript is scheduled for publication.	Protocol team members who are aware of press releases in development by pharmaceutical, biomedical industry, or external collaborators should notify the ACTG Communications Manager.	Protocol Team
Request permission to publish a press release	When study is complete and an abstract is published/presented, but final results and/or primary manuscript are not published or if primary/secondary manuscript is scheduled for publication.	Submit the press release, with a request to publish it, to ACTG Publications Office for approval by Protocol Team, SC chair, ACTG Network PI/Chair, the ACTG Communications Manager and NIAID/DAIDS.	Pharmaceutical, biomedical industry, or external collaborators, Protocol Team, or NIAID/DAIDS
Publication of press release	Following approval by protocol team, SC chair, ACTG Network PI/Chair and NIAID/DAIDS	Submit a copy of the published press release to the ACTG Publications Office.	Pharmaceutical, biomedical industry, or external collaborators, Protocol Team, or NIAID/DAIDS

Questions and comments regarding press releases may be directed to the ACTG Communications Manager, actg.communications@fstrf.org

5.0 REFERENCES

5.1 SOP ACTG-109, NWCS Development and Review

5.2 SOP ACTG-106, DACS Development and Review

5.3 SOP ACTG-126, Site Performance Measures and Standards of the Performance Evaluation Committee

5.4 SOP ACTG-107, ACTG Network-Specific Financial Disclosure and Conflict of Interest Procedures

5.5 SOP ACTG-101, Study Closure, Data Cleanup and Study Analysis Preparation

5.6 SOP ACTG-158, Requests for Data from ACTG Studies

5.7 SOP ACTG-120, Appeal and Grievance

5.8 NIH Public Access Policy at http://publicaccess.nih.gov/policy.htm.

5.9 ACTG CTU and CRS Grant numbers at https://member.actgnetwork.org/cms/folder/6211

6.0 INQUIRIES

Questions and comments regarding these procedures may be directed to the ACTG Publications Office at ACTGPublications@partners.org.

7.0 APPENDICES

Appendix 1— Writing Team Guidelines

Appendix 2— Requesting a Manuscript Writing Extension

Appendix 3— Distribution Lists

Appendix 4—Committee Reviewer Responsibilities

Appendix 5— Sanctions

Appendix 6— ACTG Publication Costs

Appendix 1: Writing Team Guidelines

Writing Team Membership

The Protocol Core Team is responsible for forming the writing team, which usually comprises the following parties—

1. Protocol Chair or Co-Chairs
2. Protocol Vice Chair(s)
3. Statisticians
4. Protocol Team investigators
5. Immunologist, virologist, and/or pharmacologist, as appropriate

Guidelines for Masthead Authorship and the Author Order

The masthead should include those who have made significant contributions to the design, conduct, or analysis of the study. Masthead authorship should not be based solely on participation as a protocol team member, data manager, CTS, laboratory staff, field representative, pharmaceutical or biomedical industry collaborators, or other external collaborators, or on the number of study participants accrued to the study. The inclusion of authors, and their roles and authorship order should be determined as the manuscript is in preparation, and finalized by the time the manuscript is ready for submission. In the event of disagreements regarding masthead authorship, the SC leadership should be consulted. If agreement cannot be reached, an appeal should be submitted to the SASC. Any subsequent appeals should follow the ACTG appeals procedure (SOP ACTG-120).

For studies that enrolled subjects from fewer than six institutions one investigator from each institution contributing study participants may be considered for masthead authorship, if journal limitations on numbers of authors will allow.

For studies involving more than six institutions, institutions with high subject enrollment may have one investigator considered for masthead authorship. The address of each co-author should reflect his/her own site. If the protocol chair or vice chair is from a high enrolling institution and is already an author, he/she can place another investigator from that institution on the masthead. In cases where the large numbers of enrollees render the inclusion of a single representative from each site with high accrual infeasible, the team may consider developing an alternative plan for allowing masthead authorship by investigators from participating sites. This plan should be presented to the SASC for consideration prior to the circulation of a draft manuscript for ACTG review.

Journal Criteria for Authors. The number of authors on the masthead of an article may be limited by journal guidelines. Masthead authorship must meet the criteria for the journal.

Masthead Author Relocation. In instances where study work is completed or substantially conducted at one institution and the author relocates to another institution prior to the manuscript being submitted to a journal, both the author's current and former institutions should be cited. It is the responsibility of the relocated author and the site leader of the former CRS to ensure that both institutions are cited in the publication.

Acknowledgment of ACTG, NIAID, and other Support for Annual Reporting and Scientific Contribution Credit

Appropriate acknowledgment of ACTG support is required for annual reporting to sponsor institutes and for ACTG-related manuscripts to receive relevant scientific contribution credit in the annual site and laboratory performance evaluations, in accordance with SOP ACTG 126, respectively.

1. In compliance with the NIH Grants Policy Statement**,** include the following citation in all papers published under the auspices of the ACTG:

   "Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1 AI068634, UM1 AI068636 and UM1 AI106701. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health". Support of collaborating Institutes or Centers (ICs), should be included with this statement, notably the National Institute of Dental and Craniofacial Research (NIDCR) and the National Cancer Institute for OHARA and malignancy studies; National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH) and National Heart, Lung and Blood Institute (NHLBI) for the studies they have supported.

2. In addition to #1, acknowledgement of the participating sites is required as follows:
   - Study-related primary and major secondary manuscripts must include an acknowledgements appendix. Please contact the ACTG Publications Office to obtain names and grant numbers from each participating site. The list of CTU and CRS Grant numbers is available on the ACTG member website under the Publications Resources page, https://member.actgnetwork.org/cms/folder/6211.
     - For studies with CRSs/CTUs that have received support from additional center grants include the following citation:

       "Supported in part by a grant(s) funded by the National Center for Advancing Translational Sciences (or subsequently designated NIH center)"
   - For NWCS and DACS and minor secondary manuscripts, a statement acknowledging the participating clinical research sites of the parent studies is sufficient.

3. Cite the ACTG's sponsor institute and all other NIH institutes that contributed funds to the ACTG's efforts.

Documentation of National Clinical Trial (NCT) Number

ACTG clinical trials are registered with the ClinicalTrials.gov web-based protocol registration system. A unique identifier (NCT number) is provided that should be documented in the final manuscript, according to the journal. The ACTG Publications Office or CTS can be contacted for this number.

Appendix 2: Requesting a Manuscript Writing Extension

If the writing team chair is not able to submit a final manuscript draft to the ACTG Publications Office within 90 days of the protocol chair receiving the final primary or secondary analysis, an additional 30-day extension may be granted by the SC Chair.

The Writing Team Chair must submit a written request for an extension to the ACTG Publications Office at least 2 weeks prior to the deadline and include an explanation for the delay. The ACTG Publications Office will forward the request to the SC chair and SC Coordinator. The SC Coordinator will subsequently provide written notification of the SC's approval or disapproval of the writing extension to the Writing Team Chair and copy the ACTG Publications Office.

If the draft manuscript is not received within 90 days of receipt of the analysis, the SC leadership may impose sanctions (See Appendix 5: Sanctions). The SC Leadership must communicate any sanctions to the ACTG Publications Office.

Appendix 3: Distribution Lists

Manuscript 14-day team review and sign-off distribution list (prior to ACTG review submission)—

For Primary/Secondary Manuscripts:

- Writing Team
- Masthead authors
- Protocol team, to include all current members including SDAC**, DAIDS***, the protocol chairs, and the pharmaceutical and biomedical industry representatives* (if applicable)
    - For substudies, the main study team & substudy team must be included

For NWCS and DACS Manuscripts:

- Masthead authors to include SDAC if SDAC** is a co-author
- Protocol Chair(s) of the parent protocol(s)
- Pharmaceutical and biomedical industry representatives of the parent protocol(s)

*If the company changes its name, merges with or is acquired by another company, a representative of the new company must receive the manuscript. Timelines and requirements for manuscript review may be superseded by Clinical Trials Agreement stipulations.

**SDAC responsibility of statistician to distribute for SDAC review; SDAC responsibility to ensure distribution of analysis reports to ACTG Network PI/Chair and Vice Chair and SC Chair and Vice Chair for both abstracts and manuscripts.)

***DAIDS responsibility of protocol member to distribute for internal DAIDS review.

The ACTG Publications Office can assist with providing the contact information for the appropriate review parties.

ACTG Publications Office manuscript review distribution list—

- SC Chair/Vice Chair/designated committee reviewer*
- ACTG Network PI/Chair
- SASC Chair
- ACTG Network Laboratory PI
- SDAC
- DAIDS
- CTU PIs or CRS Leaders of participating (for primary manuscripts only)

* If a secondary manuscript falls under a different committee than the primary manuscript, a SC chair/vice chair/designated committee reviewer from both committees must review the manuscript.

ACTG Publications Office abstract review distribution list—

- SC chair/Vice Chair/designated committee reviewer
- ACTG Network PI/Chair
- SASC Chair
- ACTG Network Laboratory PI
- DAIDS
- SDAC
- Pharmaceutical Representatives
    - For NWCS and DACS abstracts, pharmaceutical representative(s) of the contributing protocol(s)
- Protocol Chair(s) (if not on the masthead)
    - For NWCS and DACS abstracts , protocol chair(s) of contributing protocol(s)

ACTG Network Coordinating Center Executive Summary Dissemination list—

- CTU PIs and CRS leaders at participating sites (may share summary with IRB if requested)
- Protocol Team
- Director, Therapeutics Research Program, DAIDS
- DAIDS Medical Officer (clinical representative or clinical monitor)
- DAIDS Medical Officer who is a member of the SC responsible for the summary
- ACTG Network PI/Chair
- SASC Chair
- SC Chair
- ACTG Network Coordinating Center SC Leader
- SDAC Section (Scientific Committee) Head
- Industry sponsor (if sponsorship/support is listed on protocol document but no representative on the protocol team distribution list)
- Director, ACTG Network Coordinating Center
- ACTG Network Coordinating Center Clinical Manager
- ACTG Publications Office
- Regulatory Support Center for forwarding to the Food and Drug Administration
- Any site unable to retrieve the electronic information should contact the ACTG Network Coordinating Center to receive a hard copy.

Appendix 4: Committee Reviewer Responsibilities

The decision to approve or disapprove submission of a manuscript to a journal, or an abstract to a conference, is solely that of the SC chair/vice chair, or the designated committee reviewer if the chair and vice chair are conflicted.

The SC Chair/Vice Chair/designated committee reviewer is responsible for the following—

1. Ensuring the scientific integrity of the abstract or manuscript.
2. Ensuring that the writing team adheres to the ACTG publication policies on authorship; ACTG acknowledgment; citation of the protocol number(s); and citation of the NCT number.
3. Ensuring the authors have circulated the manuscript or abstract to the pharmaceutical, and biomedical industry representatives involved with the study during team review; the right to review manuscripts is an important part of the CTA between the pharmaceutical and biomedical companies and the NIAID/DAIDS, acting on behalf of the ACTG.
4. Ensuring that potential conflicts of interest are appropriately acknowledged.
5. Requiring SDAC review, if necessary
6. Confirming that primary and major secondary manuscripts are (a) credited to the ACTG Network LOC, LC, and SDAC grants (b) primarily funded by the Network and (c) contain an acknowledgement appendix containing names and grant numbers for each site. In the event that publication costs (see *Appendix 6* for details) are accrued, these criteria must be met in order for the ACTG Central Group to cover publication costs.
7. Confirming that NWCS and DACS and minor secondary manuscripts are (a) credited to the LOC, LC, and SDAC Network grants and (b) contain a statement acknowledging the participating clinical research sites.
8. Agreeing on substantial changes made to the abstract or manuscript following ACTG review.

Appendix 5: Sanctions

Manuscripts

Potential actions and/or sanctions include but are not limited to appointment of a new Writing Team Chair, deduction of scientific credit points from the relevant CRS or Specialty Laboratory during annual site and laboratory evaluations, respectively; prohibition of the writing team chair from chairing future studies and/or removal of the chair from the protocol or scientific team. In the event that another writing team chair is appointed, but is unable to complete the manuscript publication process, the responsible SC Chair will have the option to appoint a third writing team chair, or to ask the protocol statistician to prepare an Executive Summary of the study results that may be submitted to a relevant journal as a concise communication, brief report, or letter, as appropriate. This decision will be made in conjunction with the SASC and in accordance with the Executive Summary Procedures of this SOP. If a new writing team chair is appointed, the SC Coordinator is responsible for communicating the SC's new manuscript timeline to the new writing team chair and the ACTG Publications Office.

In the event that an author prefers to submit to a journal that consistently does not comply with the NIH timeline for submitting articles to PMC, the SC Chair and/or Network Leadership have the option to restrict the writing team from submitting the manuscript to the referenced journal.

Appendix 6: ACTG Publication Costs

The ACTG Central Group will cover the following publication costs for primary and secondary manuscripts if the SC Chair confirms that they have been (a) primarily funded by the Network, (b) credited to the ACTG Network LOC, LC and SDAC grants, and (c) deposited and signed off by the lead author in the PMC system. *

- Review fees
- Page charges

Any additional author fees charged for approved manuscripts, including costs for publishing in an Open Access journal and charges for color figures, will be reviewed by the Executive Committee and SASC Chairs on a case-by-case basis.

The ACTG will not cover Open Access costs for publishing in journals that do not require Open Access. If submitting a request for the ACTG to cover Open Access costs in a journal that requires Open Access, justification for submitting to an Open Access journal must be provided. If the publication cost is for a color figure(s), provide justification for publishing in color.

The ACTG Central Group will not cover publication costs for NWCS/DACS manuscripts.

Once confirmation is received indicating that the ACTG Central Group will cover the publication costs, the ACTG Publications Office will provide the author with information for the invoice.

Costs associated with ordering reprints will not be covered by the ACTG and remain the responsibility of the author.

*For Method A journals, a signed copy of the copyright transfer agreement as evidence that the publication was NIH supported and confirmation from the publisher on submission date will suffice.

FIRST AMENDMENT
TO THE CLINICAL TRIAL AGREEMENT FOR PROTOCOL ACTIV-2/A5401
BETWEEN
DIVISION OF AIDS (DAIDS),
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)
AND
ASTRAZENECA PHARMACEUTICALS LP

Subject to full execution, this First Amendment ("Amendment") is made effective as of the date of last signature ("Effective Date"), by and between AstraZeneca Pharmaceuticals LP ("Company"), having its principal address at 1800 Concord Pike, Wilmington, DE 19803, and the National Institute of Allergy and Infectious Diseases ("NIAID"), National Institutes of Health (NIH), which is part of the United States Government Department of Health and Human Services (HHS), as represented by the Division of AIDS ("DAIDS"), ["NIAID (DAIDS)"], having its principal address at 5601 Fishers Lane, Bethesda, Maryland 20852, (each a "Party" and together, the "Parties").

WHEREAS, the Parties entered into and executed a Clinical Trial Agreement for the Protocol referenced above, effective December 16, 2020 ("Agreement");

WHEREAS, the Parties desire to revise the language in the Agreement regarding the Clinical Study Report (including the appendices) and the study data; and

WHEREAS, the Parties have the authority to amend the Agreement pursuant to its terms.

NOW, THEREFORE, in consideration of the premises, the mutual covenants contained herein and other valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereby agree as follows:

1. Capitalized terms used and not otherwise defined herein will have the meanings ascribed to them in the Agreement to the extent defined therein.

2. The definition of "ICH" in Section 1 of the Agreement shall be deleted in its entirety and replaced with the following:

   ""**ICH**" means the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Cited is:

   ICH E6: "Good Clinical Practice: Consolidated Guidance," published in the Federal Register [83 Federal Register 8882 (2018)]. Also referred to as "FDA Good Clinical Practice Guidelines.""

3. Section 11.3 of the Agreement shall be deleted in its entirety and replaced with the following:

"11.3 Following finalization of study data through study Day 28 in Phase II of the Clinical Trial, NIAID (DAIDS) will release the SDTM data and associated documents identified in Appendix 7 ("Deliverables") related to the Study Product and concurrently randomized placebo study arms to Company. In turn, Company will release ADaM data and Tables, Listing and Figures (TLFs) derived from the SDTM data that are to be incorporated in the Clinical Study Report ("CSR") to NIAID (DAIDS) within sixty (60) to ninety (90) days of receipt of the SDTM data."

4. Section 11.5 of the Agreement shall be deleted in its entirety and replaced with the following:

   "11.5 NIAID (DAIDS) will authorize PPD to transfer to Company SDTM's related to the Study Product and control in a machine-readable format to be determined jointly by the Parties. If Company requires that the data be provided in a customized format(s), Company will pay for all costs associated with the customized data format(s)."

5. Section 11.7 of the Agreement shall be deleted in its entirety and replaced with the following:

   "11.7 NIAID (DAIDS) will authorize PPD to provide the following to Company to facilitate Company's preparation of the CSR: CSR Statistical Analysis Plan; blinded SDTM data sets (no shared placebo); unblinded SDTM data sets (includes shared placebo); SDTM specifications; and CSR appendices. Company will provide a copy of the CSR to NIAID (DAIDS) at least seven (7) business days prior to submission for review and comment. If significant issues are uncovered during review, additional time may be requested and mutually agreed to by the Parties."

6. Section 25.1 of the Agreement shall be deleted in its entirety and replaced with the following:

   "25.1 Unless terminated sooner in accordance with this Term and Termination Section, this Agreement will expire upon completion of the Clinical Trial activities."

7. Except as expressly amended by this Amendment, the Agreement shall be unchanged and shall remain in full force and effect in accordance with its terms.

8. This Amendment may be executed in one or more counterparts, each of which will be deemed an original, and all of which together will constitute one and the same instrument.

SIGNATURES BEGIN ON THE NEXT PAGE

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their duly authorized representatives to be effective as of the Effective Date.

Elizabeth S. Church -S Digitally signed by Elizabeth S. Church -S
Date: 2021.10.08 13:27:02 -04'00'

(Signature) (Date)

Peter S. Kim, M.D.
Director
Therapeutics Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health

(b)(6)

Oct 11, 2021

(Signature) (Date)

(b)(6)

Authorized Signatory
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19803

Appendix 7

Deliverables from PPD/NIAID (DAIDS) to Company:

1. Input into the body of Clinical Study Report (CSR)
2. ICH GCP CSR Appendixes 16.1.x:
    a. 16.1.1 Protocol and protocol amendments
    b. 16.1.2 Sample Case Report Form
    c. 16.1.3 Independent Ethics Committees/Institutional Review Boards consulted, and samples of written Subject Information and Consent Form
    d. 16.1.4 Personnel and administrative structure in the study
    e. 16.1.5 Signatures
    f. 16.1.6 Listing of subjects receiving the various batches of investigational product(s)
    g. 16.1.7 Randomisation scheme and codes
    h. 16.1.8 Audit certificates
    i. 16.1.9 Documentation of statistical methods and supporting statistical analysis
    j. 16.1.10 Documentation of inter-laboratory standardisation methods, and related quality assurance
    k. 16.1.11 Publications based on the study
    l. 16.1.12 Important Publications Referenced in the Report
    m. 16.1.13 Additional study documents
3. CSR Appendix 16.3 Case Report Forms
4. Blank CRF and SDTM specification
5. SDTM datasets and SAS programs (pending execution of a SAS Licensing Agreement)
6. Pinnacle-21 report

Deliverables from Company to NIAID (DAIDS)/PPD:

1. Primary Day 28 Analysis – Including Interim ADaMs, TFLs and CSR
2. End of study Week 72 Analysis – Including Final ADaMs, TFLs and CSR
3. ADaMs, TFLs and CSRs

IND/RA SPONSOR: NIAID (DCR)

CLINICAL TRIAL AGREEMENT

BETWEEN

DIVISION OF CLINICAL RESEARCH (DCR), NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

&

ASTRAZENECA PHARMACEUTICALS LP

Based on

Protocol ACTIV3/INSIGHT014

A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of
the Safety and Efficacy of Investigational Therapeutics for
Hospitalized Patients with COVID-19
Short Title: Therapeutics for Inpatients with COVID-19 (TICO)

The **National Institute of Allergy and Infectious Diseases ("NIAID")**, an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the **Division of Clinical Research ("DCR")** and **AstraZeneca Pharmaceuticals LP** (the "Company"), located at 1800 Concord Pike, Wilmington, DE 19803 (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial which is designated internally by the Company as an Indication Seeking Externally Sponsored Research Study (ESRI) designated as Protocol **ACTIV3/INSIGHT014**, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)."

This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). NIAID (DCR) will conduct this Clinical Trial with a consortium of clinical trial networks under the leadership and coordination of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). Other participating networks include the AIDS Clinical Trials Group (ACTG) under the terms of their Award with NIAID, as well as the Prevention and Early Treatment of Acute Lung Injury (PETAL) and the Cardiothoracic Surgery Trial Network (CTSN) under the terms of their Awards from National Heart Lung Blood Institute (NHLBI), and the U.S. Department of Veterans Affairs (VA). In the event that any other Clinical Research Sites funded by NIAID are included in this Clinical Trial in order to complete enrollment, these sites will meet NIAID standards for clinical research sites conducting research sponsored by NIAID. The Clinical Research Sites and their respective Investigators are not parties to this Agreement.

This Agreement sets forth the terms and conditions under which this Clinical Trial will be conducted and managed.

Company and NIAID (DCR) agree as follows:

1. DEFINITIONS

The terms listed in this Section will carry the meanings indicated throughout this Agreement. To the extent that a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code ("U.S.C.") or the Code of Federal Regulations ("C.F.R."), the definition in the U.S.C. or C.F.R. will control to the extent that such U.S.C. or C.F.R. is applicable and/or the terms defined in U.S.C. or C.F.R. have the equivalent meaning provided in the applicable national or regional laws, regulations or rules in countries outside the United States where the Clinical Trial is conducted. Where the terms are similarly defined in the applicable technical guidelines adopted by the ICH of which the United States, the European Union and Japan are the founding members, the ICH defined terms will prevail.

"**Adverse Event**" or "**AE**" means the definition as stated in the Protocol.

"**Affiliate**" means, with respect to Company, (i) any legal entity of which the securities or other ownership interests representing fifty percent (50%) or more of the equity or fifty

percent (50%) or more of the ordinary voting power or fifty percent (50%) or more of the general partnership interest are, at the time such determination is being made, owned, controlled, or held, directly or indirectly, by such legal entity; or (ii) any legal entity which, at the time such determination is being made, is controlling or under common control with, such legal entity. As used herein, the term "control," whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract, or otherwise.

"**Agreement**" means this Clinical Trial Agreement ("**CTA**"), all executed amendments and supplements to this Agreement, and all schedules, appendices and/or addenda to this Agreement.

"Award" means any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between a Government agency and the awardee, who may subcontract with the Clinical Research Sites.

"**Case Report Form**" or "**CRF**" means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Clinical Research Sites**" means the clinical research sites designated as INSIGHT sites and any other sites described in the introductory paragraph where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Trial**" means a biomedical or behavioral research study of Human Subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, or devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. In this Agreement, Clinical Trial means the clinical trial for the Protocol.

"**Confidential Information**" means confidential scientific, proprietary, business and/or financial information, provided that Confidential Information does not include:

(a) Information that is in the public domain or subsequently enters the public domain through no fault of the receiving Party or its representatives;

(b) Information that is presently known or becomes known to the receiving Party from its own independent sources, without restriction as to confidentiality or use, from a person having the legal right to disclose the data;

(c) Information that can be established by competent proof was already known and lawfully in the possession of the receiving Party at the time of the disclosure, without restriction as to confidentiality or use;

(d) Information that is independently created or compiled by the receiving Party without reference to or use of the Confidential Information and such independent development can be documented by receiving Party with written records;

\(e) Subject in each case to the provisions in this Agreement set forth in Section 12 (Publication and Press Releases) of this Agreement, information that is reasonably

required by scientific standards for publication of the results of the Clinical Trial (including Clinical Trial methods and/or data) or any information that is necessary for other researchers to verify the results of the Clinical Trial;

(f) Information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Study Product; or

(g) Information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, or required to be disclosed by a court of competent jurisdiction or governmental authority, provided that the Party required to disclose provides the other Party with prompt written notice and an opportunity (if legally permissible) to obtain a protective order.

"**Critical Event**" means any unanticipated study-related incident that is likely to cause or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity.

"**Data and Safety Monitoring Board**" or "**DSMB**" means an independent group of experts that advises NIAID (DCR) and the Investigators. The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (2) make recommendations to NIAID (DCR) concerning the continuation, modification, or termination of the Clinical Trial.

"**Effective Date**" means the date of the last signature of the Parties executing this Agreement.

"**Electronic Common Technical Document**" or "**eCTD**" means the standard format for electronic regulatory submissions as per 21 U.S.C. § 379k-1, "Electronic Format for Submissions," and as further described in FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," 80 Federal Register 26057 (2015).

"**FDA**" means the U.S. Food and Drug Administration.

"**Government**" means the Federal Government of the United States of America.

"**Health Authority**" or "**HA**" means any non-U.S. Health Authority used when the Clinical Trial is being conducted in whole or in part at a non-U.S. Clinical Research Site requiring the use of non-U.S. regulatory agencies.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. § 46.102(e)(1), a living individual about whom an Investigator conducting research:

(a) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimen; or

(b) Obtains, uses, studies, analyzes or generates Identifiable Private Information or identifiable biospecimens.

"**ICH**" means the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Cited are:

ICH E2F: "Development Safety Update Report", including the latest finalized revision, if any.

ICH E3: "Structure and Content of Clinical Study Reports."

ICH E6: "Good Clinical Practice: Consolidated Guidance," published in the Federal Register [83 Federal Register 8882 (2018)]. Also referred to as "FDA/HA Good Clinical Practice Guidelines."

ICH Q7: "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" published in the Federal register (66 Federal Register 49028-9 (2001)), including the latest finalized revision, if any.

"**Identifiable Private Information**" or "**IPI**" about a Human Subject means private information from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**Identifiable, Sensitive Information**" (ISI) means, in accordance with the definition of 42 U.S.C. 241(d)(4), information that is about an individual and that is gathered or used during the course of research as described in 42 U.S.C. 241(d)(1)(A) through which an individual is identified, or that includes IPI, or for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

"**IND**" means an "**Investigational New Drug Application**," filed in accordance with 21 C.F.R. Part 312, under which clinical investigation of an experimental drug or biologic (Study Product) is performed in Human Subjects in the U.S., or intended to support a U.S. licensing action.

"**INSIGHT**" means the International Network for Strategic Initiatives in Global HIV Trials funded under combination of (1) a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI) and (2) an Award from NIAID to the University of Minnesota.

"**Informed Consent Form**" means a written document that, when voluntarily signed by a Human Subject, confirms such Subject's willingness to participate in a particular clinical trial after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. A valid informed consent form satisfies the requirements of ICH E6, 45 C.F.R. Part 46 and 21 C.F.R. Part 50, as well as the requirements of 45 C.F.R. § 164.508 where the trial is conducted in the United States and by Investigators subject to

HIPAA.

"**Institutional Review Board**" ("**IRB**") or "**Independent Ethics Committee**" ("**IEC**") means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects, and 21 C.F.R. Part 56, Subpart C: IRB Functions and Operations, as amended April 1, 2013, and other applicable regulations, an independent body comprising medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of the Human Subjects involved in a clinical trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**Invention**" means any invention or discovery that is or may be patentable or otherwise protectable under Title 35 of the U.S.C.

"**Investigator**" means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Study Product to a Human Subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, Investigator means the individual(s) identified as responsible for the conduct of the Clinical Trial at any of the participating Clinical Research Sites.

"**Investigator's Brochure**" or "**IB**" means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Study Product, including animal screening, preclinical toxicology and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the Study Product or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Study Product.

"Leidos Biomedical Research" means the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory activities related to NIAID (DCR)'s clinical research. Leidos operates pursuant to a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI).

"**Manufacturing Know-How**" means all of the Company's proprietary information about the facilities, processes, or articles used in the manufacturing, processing and packaging of the Test Article. Manufacturing Know-How, that is does not fall within exclusions (a)-(d) of the definition of Confidential Information above, is the Confidential Information of Company.

"**Office for Human Research Protections**" or "**OHRP**" means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"**Patent**" means any issued U.S. patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

"PETAL" means Prevention and Early Treatment of Acute Lung Injury, a clinical trials network funded by NHLBI in accordance with the terms of an Award..

"**Protected Health Information**" or "**PHI**," has the meaning of that term as defined in 45 C.F.R. 160.103,which is a subset of *individually identifiable* health information, as also defined therein. *Identifiable* refers not only to data that is explicitly linked to a particular individual; it also includes health information with data items which reasonably could be expected to allow individual identification.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV3/INSIGHT014, "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)" and any company/product specific associated appendices. The Protocol describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. The Agreement will be governed by the most recent version of the Protocol, and should the Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement, the terms of the Agreement will govern.

"**Protocol Team**" means the team responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. The Protocol Team will include the protocol chair (an Investigator), representatives from Company, other Investigators, representatives from NIAID (DCR), and the persons involved with statistical and data analysis for the Clinical Trial. Participation on the Protocol Team will be as agreed by the Parties and will take into account any special requirements of the Protocol design.

"**Regulatory Application**" or "**RA**" means an IND-equivalent, non-U.S. Regulatory Application, applicable when the Clinical Trial is being conducted in whole or in part at a non-U.S. clinical research site.

"**Sponsor**" means, in accordance with the definition in 21 C.F.R. § 312.3 or the equivalent definition set out in the applicable laws and regulations (as well as ICH E6), an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with Study Product. The Office of Clinical Research Policy and Regulatory Operations within the NIAID Division of Clinical Research is the IND/RA holder and sponsor of record for this agreement. Additionally, in accordance with 21 C.F.R. § 312.52(a), several sponsor responsibilities will be transferred to the University of Minnesota Statistical and Data Management Center and to Leidos Biomedical Research.

"**Statistical and Data Management Center**" or "**SDMC**" means the center at the University of Minnesota responsible for providing statistical and data management services for INSIGHT clinical trials, including the Clinical Trial that is the subject of this Agreement in accordance with the terms of a subcontract from Leidos of a NIAID statement of work contained within an Award between Leidos and the National Cancer Institute (NCI). The SDMC subcontracts with International Coordinating Centers (ICCs) that work with clinical sites in many different countries and with a drug distribution company that has drug depots in the United States and the United Kingdom. References to the SDMC in this document refer to the University of Minnesota and the ICCs and drug distribution company with which they subcontract.

"**Study Product**" means, in accordance with 21 C.F.R. § 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301, *et seq*., Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended. In this Agreement, the anti-SARS-CoV-2 monoclonal antibody cocktail AZD7442 is referred to as the "Study Product."

"VA" means the U.S. Department of Veterans Affairs.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 Company acknowledges that NIAID and NHLBI fund the Clinical Research Sites under Awards, and therefore, the Clinical Research Sites have certain existing contractual or other legal obligations to NIAID and NHLBI.

2.2 Company will not provide any funding or material for any aspect of the Clinical Trial to any Clinical Research Site participating in the Clinical Trial without prior written notification to NIAID (DCR). In addition, subject to Section 14.4 of this Agreement, Company will not enter into any separate agreements, including, but not limited to, material transfer agreements, with the Clinical Research Sites or the Investigators at the Clinical Research Sites that interfere with the conduct of this Clinical Trial.

2.3 NIAID will comply with all applicable U.S. and foreign government, state and local laws, regulations and guidelines in the performance of its obligations hereunder. NIAID will ensure that its contractors and subcontractors comply with the terms of this agreement. Irrespective of where the Clinical Trial is conducted, NIAID, through its delegate(s), shall ensure that any organization, person or investigator engaged by it are appropriately qualified and experienced to perform services concerning the Clinical Trial. NIAID, through its delegate(s), shall ensure that Clinical Research Site and its personnel, including the Investigator, are not restricted or prevented under any healthcare or medicines law from taking part in clinical research activities and NIAID will not knowingly use in any capacity the services of any person who is so restricted or prevented under any such laws with respect to services to be performed under this Agreement. NIAID may delegate regulatory

obligations to one or more third parties. Without limiting the foregoing, NIAID (DCR) hereby certifies that it did not and will not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:
(i) debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or
(ii) suspended by OHRP as a clinical research site under 45 C.F.R. Part 46; or
(iii) excluded or otherwise rendered ineligible to participate in federal healthcare programs or federal procurement or non-procurement programs.

2.3.2 Any person convicted of a felony under federal law for conduct:
(i) relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application (NDA), Biologics License Application (BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or
(ii) otherwise relating to the regulation of any drug product or medical device under the FDCA.

2.3.3 Any person performing services in connection with this Clinical Trial who has been disqualified as a clinical investigator under 21 C.F.R. § 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required by 21 C.F.R. § 312.53.

2.4 If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party immediately.

2.5 The Awards require that the Investigators at Clinical Research Sites conduct the Clinical Trial in accordance with applicable provisions of ICH E6: FDA/HA Good Clinical Practice Guidelines, and requires that they comply with all applicable U.S., foreign government, state and local laws, regulations and guidelines.

2.6 Company agrees that this Protocol will be conducted only at sites as defined by NIAID (DCR), SDMC and collaborating networks. However, Company can conduct, at its own expense and under its own IND/RA, additional clinical trials with the Study Product, at non-ACTIV-3 sites. Company agrees to inform NIAID (DCR) in writing of any other clinical trials it may support for the use of the Study Product that would compete with this Clinical Trial for the same Human Subject population.

2.7 If Protocol-specified assays expected to be included in a regulatory submission are performed in laboratories not monitored by NIAID (DCR), Company warrants that such laboratories will comply with Good Clinical Laboratory Practice (GCLP) and all applicable regulatory requirements. Company will provide NIAID (DCR) with results of such assays and, upon request, provide documentation to support that the testing and laboratory

operations are compliant with GCLP and all applicable regulatory requirements. NIAID (DCR), through its contractor, may audit the laboratory(ies) to ensure compliance with GCLP and all applicable regulatory requirements.

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND/RA.** NIAID (DCR) will be responsible for the submission of an IND/RA covering the Protocol to the FDA/HA. The IND/RA will satisfy all of the requirements of the FDA/HA, and, as applicable, will comply with eCTD format requirements. Company agrees to provide all requested documents to NIAID (DCR) in eCTD format. To the extent permissible under applicable laws and regulations, Company will provide a letter granting the FDA/HA permission to cross-reference Company's pertinent Master File (MF), New Drug Application (NDA), Biologics License Application (BLA), and/or INDs/RAs in support of the NIAID (DCR)'s IND/RA, and in return, NIAID (DCR) will also provide a letter to Company, if requested, granting the FDA/HA permission to cross-reference the IND/RA filed by NIAID (DCR) for this Clinical Trial. NIAID (DCR) will provide a copy of all IND/RA submissions to Company at the time they are submitted to the FDA/HA. Any Confidential Information of another party will be removed. Where the concept of DMF is not applicable to biological substances in relation to the IND/RA submitted outside the United States, and Manufacturing Know-How is required to be disclosed in full to support such IND/RA, NIAID shall ensure its officers, agents, contractors, and collaborators directly concerned with the carrying out of this Agreement and having access to such Manufacturing Know-How, comply with the requirements set out in Section 11 to protect such Manufacturing Know-How that are Confidential Information of the Company from unauthorized use or disclosure. As set forth more fully in Section 11, NIAID undertakes to treat as strictly confidential and not to disclose to any third party any Manufacturing Know-How that are Confidential Information of the Company except as required to fulfill its regulatory obligations as Sponsor without the Company's express written permission.

3.2 NIAID (DCR) may delegate regulatory obligations to one or more third parties to facilitate NIAID's oversight, monitoring, and administration of the Clinical Trial at Clinical Research Sites outside of the United States. NIAID (DCR)'s third party delegate(s) will submit any clinical trial application and subsequent reports to all applicable HAs outside of the United States.

3.3 **Clinical Research Site Monitoring.** NIAID (DCR) or their designeee, will be responsible for Clinical Research Site monitoring in accordance with the clinical monitoring plan. Monitoring will be done in compliance with applicable provisions of the FDA/HA Good Clinical Practice Guidelines (ICH) (E6). NIAID (DCR) will communicate any Critical Event findings from clinical monitors to Company in a timely manner.

3.4 **Quality Audits**. If required by the FDA/HA and upon reasonable prior notice, the Company may perform quality audit visits and will coordinate those visits with Division of Clinical Research, NIAID, the SDMC and its ICCs, the leaders of the PETAL and CTSN networks, and the relevant Clinical Research Site staff.

3.5 Adverse Event Reporting.

3.5.1 NIAID (DCR) will collect Adverse Event reports according to the procedure outlined in the Protocol and in timeframes consistent with 21 C.F.R. § 312.32. The Clinical Research Sites will report Adverse Events to NIAID (DCR) in a timely manner and in accordance with the Protocol and Protocol Instruction Manual. NIAID (DCR) will assume responsibility for the reporting of Adverse Events to the FDA/HA and will provide copies of all of the safety reports to Company. Such reports will be sent to:

AstraZeneca Patient Safety (Pharmacovigilance)
AstraZeneca Pharmaceuticals LP
1800 Concord Pike, Wilmington, DE 19803
E-mail: AEMailboxClinicalTrialTCS@astrazeneca.com

3.5.2 NIAID (DCR) will report all unexpected Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the FDA/HA and Company on a timely basis consistent with 21 C.F.R. § 312.32 and the Protocol. NIAID (DCR) will report other serious and non-serious adverse events to the FDA/HA and to Company on a timely basis consistent with 21 C.F.R. § 312.33 and the Protocol.

3.5.3 NIAID (DCR) will report all Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the Company at the Safety Reports Address listed in the Contacts section within fifteen (15) days of awareness. Company agrees not to contact the Clinical Research Sites directly for information related to Adverse Events. Company shall contact the NIAID (DCR) Safety Office for information related to SAEs.

3.5.4 As the manufacturer, Company will, in a timely manner consistent with FDA/HA requirements and during the term of this Clinical Trial, provide NIAID (DCR) with any information it now has or may obtain in the future regarding the safety and/or the toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial. NIAID (DCR) will promptly transmit that information to all Investigators. Such information shall be sent to:

NIAID Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-846-5301
Fax: 301-846-6224
Email: rchspsafety@mail.nih.gov

3.5.5 During the course of the study, if Company is requested by a regulatory agency to unblind an SAE or SUSAR report, the NIAID (DCR) will collaborate with

Company to determine whether the report can be unblinded without undermining the scientific integrity of the Clinical Trial. NIAID (DCR) will provide the blinding codes for study subjects randomized to the Study Product or the placebo to the Study Product to Company when all data forms have been keyed into the database for all subjects, data cleaning has been completed, and the Protocol Team has declared the study data set to be complete

3.6 **Pregnancy Reporting.** NIAID (DCR) will report pregnancies with respect to Study Product to Company no later than thirty (30) days of becoming aware of such events.

4. SAFETY MONITORING

Data and Safety Monitoring Board (DSMB). A NIAID DSMB will monitor this Clinical Trial as described in the Protocol. NIAID will notify Company in advance of any DSMB review. NIAID will provide recommendations derived from the DSMB to Company. Prior to the Completion of the Clinical Trial, closed DSMB data and reports prepared for the DSMB review will be used only for the purposes of the DSMB meeting and will be held in confidence by the DSMB. Open DSMB reports will be shared with the study team.

5. FDA/HA MEETINGS/COMMUNICATIONS

5.1 With respect to any discussions with the FDA/HA involving data obtained from this Clinical Trial under NIAID (DCR)'s IND/RA, NIAID (DCR), in consultation with Company, will take the initiative in arranging meetings or conference calls with the FDA/HA. Formal meetings with the FDA/HA concerning the Clinical Trial design and/or data will be discussed and agreed upon in advance by Company and NIAID (DCR). Company will have the right to participate in all formal meetings with the FDA/HA. Company agrees not to contact the FDA/HA independently of NIAID (DCR) concerning this Clinical Trial. However, Company may contact the FDA/HA on separate product-related issues. NIAID (DCR) will provide Company with copies of all transmittal letters for IND/RA submissions, and formal questions and responses that have been submitted to the FDA/HA. Any Confidential Information of another party will be removed.

5.2 Company will promptly notify NIAID (DCR) of:

(a) Any FDA/HA correspondence related to the Protocol that is received by Company, or its Affiliates; and
(b) FDA/HA enforcement actions directed toward Company or its Affiliates, including, but not limited to, warning letters, seizures, or recalls; injunctions/consent decrees; rejection of regulatory submissions or withdrawal of approval for a product; and
(c) Criminal investigations; and
(d) Proceedings to debar Company or its Affiliates or individuals employed under a contract to Company and/or its Affiliates.

5.3 Company will also promptly notify NIAID (DCR) of any action taken by the FDA/HA regarding manufacturing of the Study Product that would impact the safety of Human Subjects in the Clinical Trial.

6. MANUFACTURE, SUPPLY, TRANSPORT, DISTRIBUTION AND USE OF STUDY PRODUCT

6.1 **Manufacture.** Company will ensure that the manufacture and/or packing, and analysis of Study Product is in compliance with GMP and the relevant Company submissions. The proposed use of a contractor by Company for the manufacture and/or packing, analysis or warehousing of Study Product shall be the responsibility of Company. Company will retain batch documentation in accordance with GMPs as defined in the Company retention policy.

6.2 **Release.** NIAID (DCR) and SDMC are responsible for the final release the Study Product including final Qualified Person Certification as defined in EEC Directive 2001/83/EEC. Company shall provide the NIAID (DCR) and SDMC with ~~a~~ supporting release documents including a Certificate of Conformity and Certificate of Analysis for the Study Product. Where requested, the Company shall provide a Qualified Person Confirmation for partially manufactured drug product confirming compliance to Good Manufacturing Practice (GMP) and to the Company IMPD/IND.

6.3 Supply. NIAID (DCR) and the SDMC shall provide Company with an estimate of the quantity of Study Product that will be required to complete the Protocol. Company will supply the Study Product to NIAID (DCR) without charge and in quantities and conditions sufficient to complete the Protocol (reasonably in line with the agreed estimations) and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Study Product.

Company will be responsible for labeling the Study Product, and any outer cartons, used in the Clinical Trial prior to shipment of Study Product to the drug distribution company under contract with the SDMC. The drug distribution company is responsible for shipping Study Product to Clinical Research Sites.

6.4 **Distribution.**

6.4.1 Company will ship the Study Product to central distribution drug depot(s) to be arranged by NIAID and the SDMC, as mutually agreed by the Parties. Company will provide specific storage and/or shipping instructions for the Study Product to NIAID (DCR), the SDMC, the central distribution drug depot(s), and/or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. Company warrants that any packaging for hazardous material, provided by Company, meets Department of Transportation regulatory requirements for use at all Clinical Research Sites.

6.4.2 The Study Product must be received by the central distribution drug depot(s) in usable condition and accompanied by Material Safety Data Sheet (MSDS), specific storage and shipping instructions, stability and/or expiration dating information, Certificate of Analysis (CoA) and the Certificate of Compliance (CoC). Specific monitoring devices shall be consigned with the Study Product to verify the required conditions have been met.

6.4.3 If there is evidence that the Study Product that arrived at the central distribution drug depot(s) has not been maintained according to the defined shipping instructions, or is potentially adulterated, the SDMC or central distribution drug depot will contact Company to inform it of the condition of the received Study Product and to determine if the Study Product is usable or if it must be replaced. If the Study Product must be replaced, Company will replace it at no cost to NIAID (DCR), the central distribution drug depot(s).

6.5 **Use.** NIAID (DCR) and the SDMC will be responsible for ensuring that the Study Product is transported to the study sites under the conditions specified by Company. NIAID (DCR) and the SDMC will not transfer the Study Product to parties other than the central distribution drug depot(s) or the Clinical Research Sites , nor will NIAID (DCR) or the SDMC chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed in writing by the Parties. NIAID (DCR), pursuant to the Awards, will ensure that the Investigators: (i) use the Study Product only in accordance with the Protocol and for no other purpose; (ii) do not transfer the Study Product to any parties except Company, the central distribution drug depot(s), or the Clinical Research Sites; and (iii) do not chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed to, in writing, by the Parties.

6.6 **Study Product Destruction.** Upon completion of the Protocol, NIAID (DCR) and the SDMC, will ensure destruction of any unused Study Product and provide documentation to Company.

6.7 **Warranty.** Company represents and warrants that the Study Product supplied shall be manufactured and released according to the principles of current Good Manufacturing Practice and when administered in accordance with Protocol it is suitable for human use.

6.8 **Source.**

6.8.1 In the event Company elects to terminate its development of Study Product for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to NIAID (DCR) within ninety (90) days of discontinuation then Company will provide NIAID (DCR) with Study Product sufficient to complete the Clinical Trial in the manner described in the Protocol.

6.8.2 The Parties also agree that should this Agreement be terminated prior to completion of the Protocol, the Protocol will be completed if medically appropriate. In that

event, each enrolled participant will be followed through the period outlined in the Protocol and Company will supply enough Study Product to complete the Protocol.

7. INVESTIGATOR'S BROCHURE (IB)

Company will provide a current IB in eCTD format for all applicable components of the Study Product, and any later revisions and addenda to the IB for the Study Product, including a summary of changes (SOC), to NIAID (DCR), as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Section 13 (Confidential Information) of this Agreement. Company agrees to provide NIAID (DCR) any updated version of the IB, with the SOC, within fifteen (15) days of issuance. Company will send the IB and SOC to the NIAID (DCR) to the attention of the NIAID contact for regulatory matters identified in Article 26. NIAID (DCR), through the SDMC, will distribute the IB to the Clinical Research Sites. NIAID (DCR) will address requests for IBs, including updated versions and SOCs, to:

(b)(6)
(b)(6)
E-mail: (b)(6) @astrazeneca.com

8. PROTOCOL DEVELOPMENT AND REGISTRATION

8.1 The Parties agree that enrollment in the Clinical Trial will not start until the version of the Protocol to be used has been reviewed in advance by Company, accepted by the Protocol Team, approved by the relevant IRB(s)/IEC(s) and NIAID (DCR) in writing, submitted to the FDA/HA, and any clinical hold issues have been responded to satisfactorily.

8.2 The Parties agree that any alteration in or amendment to the Protocol must be accepted by the Protocol Team, approved in writing by the relevant IRB(s)/IEC(s) and NIAID (DCR), and submitted to the FDA/HA prior to such alteration or amendment becoming effective.

8.3 **Protocol Registration.** All NIAID (DCR)-sponsored network protocols which include the informed consent must meet all federal mandates as well as NIAID (DCR) requirements to ensure the welfare of Human Subjects in the Clinical Trial.

Each Clinical Research Site, prior to participating in any NIAID (DCR)-sponsored study, must submit its informed consent to the NIAID (DCR) or designee for review.

9. CASE REPORT FORM DEVELOPMENT

NIAID (DCR), through the SDMC, will be responsible for the development and subsequent revisions, if any, of the Case Report Forms with appropriate review and comment by the Protocol Team.

10. HUMAN SUBJECTS PROTECTION

10.1 NIAID (DCR) and Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The informed consent of each Human Subject participating in the Clinical Trial at a Clinical Research Site will be obtained prospectively using an informed consent process. The sample informed consent document may be reviewed in advance by Company and shall be approved by NIAID (DCR) and all appropriate IRB(s)/IEC(s).

10.2 NIAID (DCR) and Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46, Protection of Human Subjects. Therefore:

10.2.1 NIAID (DCR) and Company will maintain the confidentiality of IPI, including PHI, collected under the Clinical Trial.

10.2.2 To the extent permitted by the informed consent forms and applicable laws, NIAID (DCR) and Company may inspect, but not copy, Human Subjects' medical records that might also include information not directly connected to this Clinical Trial. However, NIAID (DCR) and Company agree that this information will remain confidential and will not be used for any purpose other than confirmation of Clinical Trial data or to resolve study-related injury issues.

10.2.3 NIAID (DCR) and Company agree that neither Party will use, nor will it allow its contractors to use, IPI for any purpose not stated in the Protocol, without the consent of the other Party and local site IRB/IEC approval unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative. NIAID (DCR) will be responsible for any use of IPI by any Investigators for any purpose not stated in the Protocol and authorized under the Clinical Trial Informed Consent Document except (i) for IPI developed through the use of Study Product, when such use has been approved in writing by both Parties and the appropriate IRB/IEC approval obtained, or (ii) the use is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative.

10.2.4 NIAID (DCR) and Company agree to comply with the determinations of all IRB(s)/IEC(s) overseeing this research.

10.2.5 Biospecimens and data related to biospecimens may be provided to Company at Company's request, consistent with the Protocol and in accordance with Informed Consent Form, as available and as mutually agreed to by the Parties. Biospecimens and data related to biospecimens collected or created during and after the Clinical Trial will be coded to mask the identity of the Human Subjects to whom they pertain. The Informed Consent Form currently states that biospecimens and data may be shared with Company for future research.

10.2.6 Laboratory services performed at Company/Designee laboratories will be outlined in a sample analysis plan, which will include timelines for assessment and the amount and type of samples to be sent to Company, and which will be mutually agreed to by Company and NIAID.

11. DATA COLLECTION, ANALYSIS AND MANAGEMENT

11.1 The Clinical Research Sites will be responsible for gathering the data and submitting it to the SDMC. The Protocol Team, which includes Company representatives, will be responsible for the scientific reporting of the data.

11.2 NIAID (DCR), through the SDMC, will have responsibility for the data management: collection, entry and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

11.3 It is the responsibility of both Company and the NIAID to protect the scientific integrity of the ACTIV 3 study. Doing so requires maintaining the study blind throughout the ACTIV-3 study unless the independent DSMB recommends otherwise. If the study product passes the initial futility assessment, no data will be unblinded until the target number of primary events is accrued or the DSMB recommends early termination. Following completion of primary analysis and unblinding of the data, the company will be provided with the data. If the study product does not pass the futility assessment, the DSMB may recommend unblinding of summary data on which the futility assessment was based, and, if so, the company will be provided the data. According to protocol, participants will continue to be followed through twelve (12) months and the blind will continue to be maintained for that data and the study participant and site clinical staff.

11.4 All data obtained from the Clinical Trial will be in the custody of the Investigator or the Clinical Research Site, as applicable, which produces such data. Other than Company, its contractors and its designees, no party may review or use the data obtained from the Clinical Trial for purposes of seeking regulatory approval of the Study Product without written permission of Company.

11.5 Upon completion of the data analysis for the Study Product, the NIAID will authorize the SDMC to transfer to the Company a copy of the raw data and data analysis set related to the Study Product and matched control in a machine-readable format to be determined jointly by the Parties. If Company requires that the data be provided in a customized format(s), Company will pay for all costs associated with the customized data format(s).

11.6 Subject to the right of NIAID (DCR) and the Investigators to publish the data from this Clinical Trial as set forth in the Publications and Press Releases Section of this Agreement, Company has the right to utilize the data reports from this Clinical Trial in its possession for all legitimate business or regulatory purposes. NIAID (DCR) and/or Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA/HA and the Securities and Exchange Commission

(SEC), for all legitimate public health, regulatory or business purposes. Except for information related to regulatory or safety issues or under emergency circumstances where it is not practicable to do so and to the extent permitted by law, NIAID (DCR) will not release information regarding the Clinical Trial to governmental organizations without prior notification to Company.

11.7 Company will be responsible for preparing the final Clinical Study Report in accordance with ICH E3, "Structure and Content of Clinical Study Reports" and will provide a copy of the Clinical Study Report to NIAID (DCR) and the SDMC for review and comment prior to its finalization.

11.8 Both parties acknowledge that should the study results be positive, the Company will be responsible for any and all marketing authorization submissions. Accountability and responsibility for the conduct of the Clinical Trial remains with NIAID (DCR).

12. PUBLICATIONS AND PRESS RELEASES

12.1 Any publications based on the results of the Clinical Trial and originating from NIAID (DCR) or the Investigators will conform to the latest version of the INSIGHT Publications Standard Operating Procedure. Unless requested otherwise by Company, NIAID (DCR) will acknowledge Company as the source of the Study Product in any NIAID (DCR) publication resulting from the Clinical Trial and will ensure that the Investigators do the same in their publications resulting from the Clinical Trial.

12.2 Recognizing that employees of either Party may play an important role in the design, analysis and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the generally accepted customs pertaining to authorship. NIAID (DCR) will ensure that the Investigators include appropriate individuals from both Parties in their publications resulting from the Clinical Trial.

12.3 Each Party will provide, and NIAID (DCR) will ensure that the Investigators provide, a copy of any abstract or manuscript to the other Party prior to submission for publication with sufficient time for review and comment, as outlined in the INSIGHT Publications Standard Operating Procedure [Manuscripts: ten (10) days; Abstracts: five (5) days]. The publication or other disclosure may be delayed for up to thirty (30) additional business days for manuscripts and up to five (5) business days for abstracts, upon written request by either Party as necessary to preserve U.S. or foreign Patent or other intellectual property rights. Each Party agrees that, following the receiving Party's review of the manuscript and/or abstract for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish, present or use any Clinical Trial data. Notwithstanding the timelines described above, the Parties agree that expedient publication of the Clinical Trial results is necessary for the public good and the Parties agree to work in good faith to allow expeditious publication of the Clinical Trial results.

12.4 Each Party will provide, and NIAID (DCR) will ensure that the Investigators provide, a copy of any proposed press release to the other Party for review at least five (5) business days in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish the press release provided that if the press release is not submitted by the Company, the Company may remove Company Confidential Information from such press release. If the Company requests redaction of its Confidential Information, the Company will make reasonable efforts to supply substitute non-confidential information in order to allow the press release to go forward.

13. CONFIDENTIAL INFORMATION

13.1 Either Party may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct and inform on the progress of the Clinical Trial, and will as applicable, either (i) leave fully intact any confidentiality notices places on the Confidential Information by the disclosing Party or (ii) place a confidentiality notice on all written Confidential Information. The disclosing Party will reduce confidential non-written communications to writing within thirty (30) business days of first disclosure. Oral disclosures should be reduced to writing and marked "Confidential" within thirty (30) days after disclosure to be considered Confidential Information. If a Party does not reduce oral Confidential Information to writing, the Party must verbally provide notice of the confidential nature of the oral disclosure at the time it is disclosed for the oral Confidential Information to be considered confidential under this Agreement. Notwithstanding the foregoing, Parties agree that all Manufacturing Know-How that does not fall within exclusions (a)-(d) of the definition of Confidential Information is considered Company Confidential Information. Each Party receiving Confidential Information agrees that any information so designated will be maintained as Confidential Information in accordance with this Agreement and used by it only for the purposes of the Clinical Trial. Any Party may object to the designation of information as Confidential by the other Party.

13.2 Unless expressly provided otherwise, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA), 5 U.S.C. § 552, or other applicable laws and/or regulations to disclose the Confidential Information, except that NIAID (DCR) may disclose the Company's Confidential Information to NIAID (sub)contractors to which NIAID has delegated its obligations in connection with the conduct of the Clinical Trial, Investigators, their designated Protocol staff, and site IRB solely to the extent required for the conduct of the Clinical Trial, and Company may disclose NIAID's Confidential Information to its Affiliates, its and its Affiliates' directors, representatives, agents, officers, attorneys, grantees, contractors, consultants and employees, and advisors (collectively, "Agents") to the degree necessary

to conduct the Clinical Trial. The Parties will ensure that their respective Agents maintain the confidentiality of Confidential Information in accordance with the terms of this Agreement.

13.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. Except as expressly provided in Section 13.2, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the written consent of the disclosing Party.

13.4 The Company acknowledges that some Government documents are available (with abstracts) to the public under FOIA. However, NIAID acknowledges that the Manufacturing Know-How that are Confidential Information of the Company are proprietary, commercial information of the Company and may be exempted from release under FOIA. Current NIH policy requires that a brief synopsis, the enrollment status and study results for all NIH-funded clinical trials be posted in the ClinicalTrials.gov registry of clinical studies, available through the NIH website. NIAID (DCR) shall be responsible for submitting information to ClinicalTrials.gov after review of information related to the Study Product by Company's representative on the Protocol Team, provided that the Company may remove Company Confidential Information from such posting to ClinicalTrials.gov. If the Company requests redaction of its Confidential Information, the Company will make reasonable efforts to supply substitute non-confidential information in order to allow such posting to go forward. In no event, however, will NIAID post any Manufacturing Know-How on ClinicalTrials.gov.

13.5 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given an opportunity to seek a court order to enjoin from disclosure.

13.6 If the receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Section 13.2, becomes legally required to disclose any of the Confidential Information, the receiving Party shall, to the extent practicable, consult with the disclosing Party prior to any disclosure.

13.6 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above, or three (3) years after the expiration or termination date of this Agreement. Either Party may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

14. INTELLECTUAL PROPERTY

14.1 Ownership of any invention made solely or jointly by NIAID (DCR), the Clinical

Research Sites and Investigators, or other NIAID (DCR) contractors or grantees as a consequence of conducting the Clinical Trial and involving the Study Product, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party claims by virtue of this Agreement any right, title, or interest in or to any issued Patents or pending Patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by Company to NIAID (DCR) with respect to the Study Product, other than the limited right to use the Study Product for the performance of the Protocol in accordance with the terms of this Agreement.

14.2 **NIAID (DCR) Intellectual Property.**

14.2.1 The Government will retain title to any Patent or other intellectual property rights in inventions made by NIAID (DCR) employees in the course of the Clinical Trial.

14.2.2 NIAID (DCR) agrees to notify Company of any such Invention and is willing to disclose it to Company under an appropriate confidentiality agreement. Company may apply for exclusive license rights to any patentable Invention made by NIAID (DCR) employees that might arise during the clinical research and the NIH will consider Company's application for a nonexclusive or exclusive license consistent with 37 C.F.R. Part 404.

14.3 **Company Intellectual Property.** Company will retain title to any Patent, pending patent applications, or other intellectual property rights in Inventions made by its employees during the course of the Clinical Trial.

14.4 **Clinical Research Site/Investigator Intellectual Property.** This Agreement does not grant any license or obligation to license any intellectual property of the Clinical Research Sites or preclude the creation of intellectual property rights, including, but not limited to, Inventions made by INSIGHT, the Investigators, or other Government contractors or grantees during the course of the Clinical Trial. Company may enter into a separate agreement with the Clinical Research Sites or Investigators regarding intellectual property rights and confidentiality that do not interfere with the conduct of this Clinical Trial or contradict the terms of this Agreement.

14.5 **Joint NIAID-Company Intellectual Property.** NIAID and Company will have joint intellectual property rights in Inventions made jointly by their employees during the course of the Clinical Trial. The Company may apply for a non-exclusive or exclusive license to the NIAID's rights in such Inventions in accordance with 37 CFR 404.

15. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome

by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its commercially reasonable efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

16. LIABILITY, INDEMNIFICATION AND INSURANCE

16.1 **Liability.** Activities carried out under this Agreement are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) as implemented under the amended declaration, "Public Readiness and Emergency Preparedness Act Coverage for medical countermeasures against COVID–19," issued on March 17, 2020 (85 Federal Register 15198). The PREP Act provides immunity from liability claims against manufacturers, distributors, program planners and other qualified persons ("Covered Persons") arising from the administration and use of covered countermeasures, as specified in a declaration by the Secretary of HHS ("Secretary") [See section 319F-3 of the Public Health Service Act (42 U.S.C. §247d-6d)]. The exception to this immunity is acts of willful misconduct by the Covered Persons. (i) The Study Product is considered a drug to treat, prevent or mitigate COVID-19, and as such is a covered countermeasure under the Secretary's declaration, and (ii) Company asserts that it is a "covered person" with respect to all "claims for loss" caused by, arising out of, relating to, or resulting from the "administration" or the "use" of the Study Product, which is a "covered countermeasure" against COVID-19, as set forth more fully in the PREP Act 42 U.S.C. §247d-6d(b), and the PREP Act Declaration issued by the Secretary of the Department of the Health and Human Services effective as of February 4, 2020. Informed consent forms used in the Clinical Trial will include a sufficient description of the PREP Act for participants to understand that all Covered Persons have immunity from liability under the PREP Act, and what compensation may be available under the PREP Act Countermeasure Injury Compensation Program [See section 319F-4 of the Public Health Service Act (42 U.S.C. §247d-6e)]. To the extent that PREP Act coverage is not available, each Party shall be liable for any loss, claim, damage or liability that it incurs as a result of its direct activities under this Agreement, except that NIAID (DCR), as an agency of the U.S. Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171.

16.2 **Indemnification.**

16.2.1 In view of the Anti-Deficiency Act, 31 U.S.C § 1341, NIAID cannot agree to indemnify the Company for its losses. Each Party will be liable for the losses, claims, damages, or liabilities that it incurs as a result of its activities under this Agreement except that (i) the NIAID, as an agency of the Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171, and (ii) the Company asserts that it is a "covered person" with respect to all "claims for loss" caused by, arising out of, relating to, or resulting from the "administration" or the "use" of the Test Article, which is a "covered countermeasure" against COVID-19, as set forth more fully in the Public Readiness and Emergency Preparedness Act, 42 U.S.C. §247d-6d(b) and the PREP Act Declaration issued by the Secretary of the Department of Health and Human Services effective as of February 4, 2020.

16.2.2 To the extent that PREP Act coverage is not available, Company will defend, indemnify and hold harmless the Government's grantees and contractors and their respective agents and employees "Indemnitee(s)" from any and all liabilities, damages, losses, claims, action, suits and expenses, including attorneys' fees and court costs (collectively "Claims") to the extent caused by the administration or use of the Study Product during the course of the Clinical Trial, provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if each of the following conditions is met:

a) The Claim did not arise or result from, directly or indirectly, the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, any written instructions from Company, and this Agreement.

b) The Claim was not caused by the gross negligence, recklessness or willful misconduct of any Indemnitee, provided that any action properly taken by the Indemnitee in full compliance with the Protocol or written instructions from Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if a Claim is jointly caused by the negligence of any Indemnitee and the administration or use of the Study Product, then Company will provide defense and indemnification solely to the extent the Claim was caused by the administration of the Study Product.

c) Company is promptly notified of the Claim, provided that the failure to give such notice will not abrogate or diminish Company's defense and indemnity obligation or if such failure does not prejudice Company's ability to defend the Claim.

16.2.3 Company will have sole control over the defense and settlement of the Claim(s) directed against Company.

16.2.4 Company will have the right to select defense counsel and to direct the defense and settlement of the Claim(s) directed against Company.

16.2.5 Company will provide a diligent defense against and/or settlement of any Claims for which defense and indemnification are provided under this Agreement whether such Claims are rightfully or wrongfully made. Company will have the right to settle such Claims, at Company's sole expense and in Company's sole discretion. Indemnitee(s) will fully cooperate, at Company's expense, with Company and its legal representatives in the investigation and defense of any Claim for which defense and indemnification are provided under this Agreement.

16.2.6 The Indemnitee(s) will at all times have the right to fully participate in the defense of any Claim at their own expense and for their own account. If Company fails to defend any Claim for which defense and indemnification are provided under this Agreement, after the Indemnitee(s) has given written notice setting out the reasons why it considers Company has failed to properly defend the Claim, the Indemnitee(s) will have the right, but not the obligation, to undertake the defense of and to compromise or settle the Claim on behalf, for the account, and at the risk of Company.

16.3 **Participant Injury Attributable to the Clinical Trial**. Company will pay the reasonable cost of medical care required by Clinical Trial participants for illness or injury directly attributable to the Study Product. For purposes of this determination and Company's obligation under this Agreement, "attributable" means that the receipt of the Study Product and the Clinical Trial participant's illness or injury are reasonably related in time, and the illness or injury is more likely explained by the receipt of the Study Product than another cause.

The payment or offer of payment of any amount by Company on behalf of a participant or his or her healthcare insurer or other third party payer under this Section is not an admission of fault or liability by any one or more of (a) the United States Government or any agency thereof; (b) the Clinical Research Site or its affiliate organizations, or (c) Company, its employees or agents, and any such payment or offer of payment will not be considered a waiver of any defense or other legal right by any of the foregoing in any legal, administrative or similar proceeding including the PREP Act, 42 U.S.C. §247d-6d(b) and the PREP Act Declaration issued by the Secretary of the Department of Health and Human Services effective as of February 4, 2020 and the Company reserve the right to seek reimbursement of any medical care costs advanced pursuant to this section 16.3.

16.4 **Insurance.** Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the research related injury and indemnification obligations assumed under this Agreement. Upon request, Company will provide evidence of its insurance or self-insurance to NIAID (DCR).

17. DISPUTE RESOLUTION

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the

dispute will be referred to the Director of DCR, NIAID (or his/her designee) and an appropriate authorized representative of Company for resolution. If the Director of DCR (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute through good faith negotiations within thirty (30) days, the dispute will be referred to the Director of NIAID (or his/her designee) and the authorized representative of Company. If the Director of NIAID (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute, either Party may pursue any and all administrative or judicial remedies that may be available.

18. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the other Party, enter into any contract, warranty, or representation as to any matter. Neither Party will be bound by the acts of the other Party.

19. NON-ENDORSEMENT

By entering into this Agreement, NIAID (DCR) does not directly or indirectly endorse any product or service provided, or to be provided, by Company. Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However, Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

20. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

21. SURVIVABILITY

The provisions of Sections 1 (Definitions), 2 (Clinical Research Sites and Investigators), 3 (Investigational New Drug Application Sponsorship), 6 (Supply, Distribution and Use of Study Product), 10 (Human Subjects Protection), 11 (Data Collection, Analysis and Management), 12 (Publications and Press Releases), 13 (Confidential Information), 14 (Intellectual Property), 16 (Liability, Indemnification and Insurance),17 (Dispute Resolution), 18 (Independent Contractors), 19 (Non-Endorsement), 20 (Amendments),this Section 21 (Survivability), and sub-Section 25.4 will survive the expiration or earlier termination of this Agreement.

22. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement. The provisions of this Agreement are severable and, in the event that any

provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

23. ASSIGNMENT

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without the prior permission of the other Party, provided, however, that the Company will have the right to assign this Agreement to an Affiliate upon prior written notice to the NIAID. The terms and conditions of this Agreement shall be binding on and inure to the benefit of the permitted successors and assigns of the Parties.

24. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts of the District of Columbia.

25. TERM AND TERMINATION

25.1 Unless terminated sooner in accordance with this Term and Termination Section, this Agreement will expire upon completion of all Clinical Trial activities and delivery of data analyses related to the Protocol and Study Product to the Company.

25.2 The Parties may terminate this Agreement at any time by mutual written consent.

25.3 Either Party may unilaterally terminate this Agreement at any time by giving written notice at least thirty (30) days prior to the desired termination date.

25.4 The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically or ethically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol, and Company will supply enough Study Product to complete the Clinical Trial. In the event that Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution, Company must notify NIAID (DCR) within at least thirty (30) days of the dissolution.

26. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt), Portable Document Format (PDF) or email followed by confirmational hard copies when requested.

For Company:

(b)(6)
(b)(6)
1800 Concord Pike
Wilmington, DE 19850-5437
Phone: (b)(6)
E-mail: (b)(6)@astrazeneca.com

For regulatory matters:

(b)(6)
(b)(6)
One MedImmune Way
Gaithersburg, MD 20878
Phone: (b)(6)
E-mail: (b)(6)@astrazeneca.com

For technical matters:

(b)(6)
(b)(6)
One MedImmune Way
Gaithersburg, MD 20878
Phone: (b)(6)
E-mail (b)(6)@astrazeneca.com

For NIAID (DCR):

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services
5601 Fishers Lane, Suite 6D
Rockville, MD 20892-9804
Phone: (b)(6)
Email: (b)(6)@niaid.nih.gov

For regulatory matters:

John Tierney, R.N., M.P.M
Clinical Research Oversight Manager
Office of Clinical Research Policy and Regulatory Operations
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9820
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6)@niaid.nih.gov

For clinical matters:

Elizabeth Higgs, M.D.
Global Health Science Advisor
DCR, NIAID, NIH
5601 Fishers Lane, MSC 9802
Rockville, MD 20852
Phone: (b)(6)
E-mail: (b)(6) @niaid.nih.gov

27. COUNTERPARTS

This Agreement may be executed in one or more counterparts, each of which will be deemed to be an original copy of the Agreement, and all of which, when taken together, will be deemed to constitute one and the same Agreement. Signatures to this Agreement transmitted by fax, by electronic mail in portable document (.pdf) format, or by any other electronic means intended to preserve the original graphic and pictorial appearance of the Agreement, will have the same effect as physical delivery of the paper document bearing the original signature.

SIGNATURES BEGIN ON THE NEXT PAGE

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

(b)(6)

(Signature)

12-08-2020

(Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6)

(Signature)

December 08, 2020

(Date)

(b)(6)

(b)(6)

AstraZeneca Pharmaceuticals LP

cc: Principal Investigators, Clinical Research Sites

AMENDMENT NO. 1
TO
CLINICAL TRIAL AGREEMENT

This 1st Amendment (NIAID Ref. No. 2020-1103-1) to Clinical Trial Agreement (NIAID Ref. No. 2020-1103) is made as of the date of the last authorized signature by and between AstraZeneca Pharmaceuticals LP ("Company"), and The National Institute of Allergy and Infectious Diseases ("NIAID"), an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the Division of Clinical Research ("DCR"). Each of Company and NIAID may be referred to herein as a "Party" or together as "Parties."

WHEREAS, Company and NIAID entered into a Clinical Trial Agreement, dated December 8, 2020 (the "Agreement") for the conduct of the clinical trial designated as Protocol ACTIV3/INSIGHT014, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)" ; and

WHEREAS, the Parties desire to amend the Agreement as set forth herein;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, and intending to be legally bound, the Parties hereto agree as follows:

1. Definitions. All terms used in this Amendment and not otherwise defined herein shall have the same meanings ascribed to them in the Agreement.

2. Amendments:

   a. Section 6.2 is deleted in its entirety and is replaced with the following:

      6.2 **Release.** NIAID and SDMC are responsible for the final distribution of the Study Product to a Clinical Research Site after the Clinical Research Site has satisfied the regulatory requirements, including obtaining IRB/IEC approvals, to commence administering the Study Product in the Clinical Trial. If the Study Product will be distributed to Clinical Research Sites within the European Union, release of the Study Product including final Qualified Person Certification (Qualified Person as defined in EEC Directive 2001/83/EC) will be provided by Company. Company shall provide NIAID and SDMC with release documents including a Certificate of Conformity and Certificate of Analysis ("CoA"). Where requested, and in response to documented evidence of trial approval by country, Company shall provide a Qualified Person Certification for study product for said country.

3. All other terms and conditions of the Agreement shall remain unchanged.

SIGNATURES BEGIN ON NEXT PAGE

IN WITNESS WHEREOF, each Party has caused this This 1st Amendment (NIAID Ref. No. 2020-1103-1) to Clinical Trial Agreement (NIAID Ref. No. 2020-1103) to be executed by its authorized representative.

ACCEPTED AND AGREED TO:

H. Clifford Lane — December 28, 2020

(Signature) — (Date)

H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6) — December 23, 2020

(Signature) — (Date)

(b)(6)
Authorized Signatory
AstraZeneca Pharmaceuticals LP

cc: Principal Investigators, Clinical Research Sites

AMENDMENT NO. 2
TO
CLINICAL TRIAL AGREEMENT

This 2nd Amendment (NIAID Ref. No. 2020-1103-2) to Clinical Trial Agreement (NIAID Ref. No. 2020-1103) is made as of the date of the last authorized signature by and between AstraZeneca Pharmaceuticals LP ("Company"), and The National Institute of Allergy and Infectious Diseases ("NIAID"), an institute of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), as represented by the Division of Clinical Research ("DCR"). Each of Company and NIAID may be referred to herein as a "Party" or together as "Parties."

WHEREAS, Company and NIAID entered into a Clinical Trial Agreement, dated December 8, 2020, as amended on December 28, 2020 (the "Agreement") for the conduct of the clinical trial designated as Protocol ACTIV3/INSIGHT014, entitled "A Multi-Center, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19; Short Title: Therapeutics for Inpatients with COVID-19 (TICO)" ; and

WHEREAS, the Parties desire to amend the Agreement as set forth herein;

NOW, THEREFORE, for good and valuable consideration, the receipt of which is hereby acknowledged, and intending to be legally bound, the Parties hereto agree as follows:

1. Definitions. All terms used in this Amendment and not otherwise defined herein shall have the same meanings ascribed to them in the Agreement.

2. Amendments:

   a. a. The following is added to the Agreement as Section 11.9:

      11.9 Given the nature of the SARS-CoV-2 pandemic, it is anticipated that novel genetic variants of the SARS-CoV-2 will evolve which may impact the potency and/or efficacy of the Study Product. The Parties agree to cooperate in good faith to evaluate the effects of these variants on the potency of the Study Product, including the sharing of any data that relates to the potency of the Study Product against these variants. The Company agrees to provide NIAID with sufficient Study Product to allow NIAID and/or NIAID contractors to conduct pre-clinical testing of the potency of the Study Product against any variants that arise that have the potential to impact the efficacy of the Study Product at any of the global Clinical Research Sites. NIAID will share the data generated through this testing with the Company.

3. All other terms and conditions of the Agreement shall remain unchanged.

SIGNATURES BEGIN ON NEXT PAGE

IN WITNESS WHEREOF, each Party has caused this This 2nd Amendment (NIAID Ref. No. 2020-1103-2) to Clinical Trial Agreement (NIAID Ref. No. 2020-1103) to be executed by its authorized representative.

ACCEPTED AND AGREED TO:

H. Clifford Lane — February 27, 2021

(Signature) (Date)
H. Clifford Lane, M.D.
Director, Division of Clinical Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

(b)(6) — February 24, 2021

(Signature) (Date)
(b)(6)
Authorized Signatory
AstraZeneca Pharmaceuticals LP

cc: Principal Investigators, Clinical Research Sites

CLINICAL TRIAL AGREEMENT

BETWEEN

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

&

JANSSEN BIOTECH, INC.

Based on

Protocol ACTIV-1 IM

Randomized Master Protocol for Immune Modulators for Treating COVID-19

The **National Center of Advancing Translational Sciences ("NCATS")**, a center of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), and Janssen Biotech, Inc. (the "Company"), located at 800/850 Ridgeview Drive, Horsham PA 19044, United States of America (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial designated as Protocol **ACTIV-1 IM** entitled "Randomized Master Protocol for Immune Modulators for Treating COVID-19."

This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). BARDA is funding this trial via a contract with Technical Resources International, Inc. (TRI) and has named NCATS as the TRI contract designee in which NCATS will oversee the design and implementation of the trial. NCATS will conduct this Clinical Trial with a consortium of sites selected with assistance from TRI, and their subcontractors Duke Clinical Research Institute (DCRI) and Syneos Health ("Syneos"). Sites within the United States will be selected from the Clinical and Translational Science Awards (CTSA) Program and other selected sites under the leadership and coordination of DCRI, and international sites will be selected under the leadership and coordination of Syneos. In the event that any other Clinical Research Sites are included in this Clinical Trial in order to complete enrollment, these sites will meet NCATS standards for clinical research sites conducting research sponsored by NCATS. BARDA, TRI, DCRI, Syneos and the Clinical Research Sites and their respective Investigators are not parties to this Agreement.

Company is the owner and manufacturer of the Study Product (as defined below) which is being provided for use in the Clinical Trial;

This Agreement sets forth the terms and conditions under which this Clinical Trial will be conducted and managed.

Company and NCATS agree as follows:

1. DEFINITIONS

The terms listed in this Section will carry the meanings indicated throughout this Agreement. To the extent that a definition of a term as provided in this Section is inconsistent with a corresponding definition in the applicable sections of either the United States Code ("U.S.C.") or the Code of Federal Regulations ("C.F.R."), the definition in the U.S.C. or C.F.R. will control.

"**Adverse Event**" or "**AE**" means the definition as stated in the Protocol.

"**Affiliate**" means, with respect to Company, (i) any legal entity of which the securities or other ownership interests representing fifty percent (50%) or more of the equity or fifty percent (50%) or more of the ordinary voting power or fifty percent (50%) or more of the general partnership interest are, at the time such determination is being made, owned, controlled, or held, directly or indirectly, by such legal entity; or (ii) any legal entity which, at the time such determination is being made, is controlling or under common

control with, such legal entity. As used herein, the term "control," whether used as a noun or verb, refers to the possession, directly or indirectly, of the power to direct, or cause the direction of, the management or policies of a legal entity, whether through the ownership of voting securities, by contract, or otherwise.

"**Agreement**" means this Clinical Trial Agreement ("**CTA**"), all executed amendments and supplements to this Agreement, and all schedules, appendices and/or addenda to this Agreement.

"Applicable Law" means all applicable laws, rules, regulations, guidelines or other requirements of governmental authorities, including but not limited to those that may be in effect from time to time in the United States of America with respect to the validity or enforceability of this Agreement or activities under this Agreement, as may be applicable.

"**Award**" means any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between a Government agency and the awardee, who may subcontract with the Clinical Research Sites.

"**Case Report Form**" or "**CRF**" means the data collection form(s) to be completed for each Human Subject participating in the Clinical Trial.

"**Clinical Research Sites**" means the selected clinical research sites described in the introductory paragraph where the Clinical Trial will be conducted in strict accordance with the Protocol.

"**Clinical Trial**" means a biomedical or behavioral research study of Human Subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, or devices, or new ways of using known drugs, treatments or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective. In this Agreement, Clinical Trial means the clinical trial for the Protocol.

"Company Commercial Distributors" shall mean Merck/MSD and MTPC.

"**Confidential Information**" means confidential scientific, proprietary, business and/or financial information, provided that Confidential Information does not include:

(a) Information that is in the public domain or subsequently enters the public domain through no fault of the receiving Party;

(b) Information that is presently known or becomes known to the receiving Party from its own independent sources, without restriction as to confidentiality or use, from a person having the legal right to disclose the data;

(c) Information that can be established by competent proof was already known and lawfully in the possession of the receiving Party at the time of the disclosure, without restriction as to confidentiality or use;

(d) Information that is independently created or compiled by the receiving Party without reference to or use of the Confidential Information and such independent development can be documented by receiving Party with written records;
(e) Information that is reasonably required by scientific standards for publication of the results of the Clinical Trial (including Clinical Trial methods and/or data) or any information that is necessary for other researchers to verify the results of the Clinical Trial;
(f) Information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Study Product; or
(g) Information that is required to be disclosed for compliance with applicable U.S. federal, foreign government, state or local law or regulation, or required to be disclosed by a court of competent jurisdiction or governmental authority, provided that the Party required to disclose provides the other Party with prompt written notice and an opportunity (if legally permissible) to obtain a protective order.

"**Critical Event**" means any unanticipated study-related incident that is likely to cause or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity.

"**Data and Safety Monitoring Board**" or "**DSMB**" means an independent group of experts that advises NCATS and the Investigators. The primary responsibilities of the DSMB are to: (1) periodically review and evaluate the accumulated data of the Clinical Trial for participant safety, Clinical Trial conduct and progress, and when appropriate, efficacy; and (2) make recommendations to NCATS concerning the continuation, modification, or termination of the Clinical Trial.

"**Effective Date**" means the date of the last signature of the Parties executing this Agreement.

"**Electronic Common Technical Document**" or "**eCTD**" means the standard format for electronic regulatory submissions as per 21 U.S.C. § 379k-1, "Electronic Format for Submissions," and as further described in FDA Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications," 80 Federal Register 26057 (2015).

"**FDA**" means the U.S. Food and Drug Administration.

"**Government**" means the Federal Government of the United States of America.

"**Health Authority**" or "**HA**" means any non-U.S. Health Authority used when the Clinical Trial is being conducted in whole or in part at a non-U.S. Clinical Research Site requiring the use of non-U.S. regulatory agencies.

"**Human Subject**" means, in accordance with the definition in 45 C.F.R. § 46.102(e)(1), a living individual about whom an Investigator conducting research:

(a) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies or analyzes the information or biospecimen; or

(b) Obtains, uses, studies, analyzes or generates Identifiable Private Information or identifiable biospecimens.

"**ICH**" means the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Cited are:
ICH E3: "Structure and Content of Clinical Study Reports."
ICH E6: "Good Clinical Practice: Consolidated Guidance," published in the Federal Register [83 Federal Register 8882 (2018)]. Also referred to as "FDA/HA Good Clinical Practice Guidelines."

"**Identifiable Private Information**" or "**IPI**" about a Human Subject means private information from which the identity of the Human Subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

"**IND**" means an "**Investigational New Drug Application**," filed in accordance with 21 C.F.R. Part 312, under which clinical investigation of an experimental drug or biologic (Study Product) is performed in Human Subjects in the U.S., or intended to support a U.S. licensing action.

"**Institutional Review Board**" ("**IRB**") or "**Independent Ethics Committee**" ("**IEC**") means, in accordance with 45 C.F.R. Part 46, Protection of Human Subjects, and 21 C.F.R. Part 56, Subpart C: IRB Functions and Operations, as amended April 1, 2013, and other applicable regulations, an independent body comprising medical, scientific and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of the Human Subjects involved in a clinical trial. It may also be referred to as an Independent Ethics Committee in accordance with ICH E6, Section 1.27.

"**Invention**" means any invention or discovery that is or may be patentable or otherwise protectable under Title 35 of the U.S.C.

"**Investigator**" means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Study Product to a Human Subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. In this Agreement, Investigator means the individual(s) identified as responsible for the conduct of the Clinical Trial at any of the participating Clinical Research Sites.

"**Investigator's Brochure**" or "**IB**" means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Study Product, including animal screening, preclinical toxicology and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior

experience with the Study Product or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the Study Product.

"**Office for Human Research Protections**" or "**OHRP**" means the HHS office that oversees protection of human subjects from research risks under 45 C.F.R. Part 46 (the Common Rule).

"**Patent**" means any issued U.S. patent, any international counterpart(s), and any corresponding grant(s) by a non-U.S. government in place of a patent.

"**Protected Health Information**" or "**PHI**," as defined in 45 C.F.R. Parts 160 and 164, under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), includes any *individually identifiable* health information. *Identifiable* refers not only to data that is explicitly linked to a particular individual; it also includes health information with data items which reasonably could be expected to allow individual identification.

"**Protocol**" means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV-1 IM, "Randomized Master Protocol for Immune Modulators for Treating COVID-19" and any company/product specific associated appendices. The Protocol describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial. For the purposes of this Clinical Trial, the term Protocol includes any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the Clinical Trial. The Agreement will be governed by the most recent version of the Protocol, and should the Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement, the terms of the Agreement will govern.

"**Protocol Team**" means the team responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification as more fully described in Appendix 4. The Protocol Team will include the protocol chair (an Investigator), representatives from Company, other Investigators, representatives from NCATS, TRI and the persons involved with statistical and data analysis for the Clinical Trial. Participation on the Protocol Team will be as agreed by the Parties and will take into account any special requirements of the Protocol design.

"Reference Safety Information" means safety information by which a Party listedness/expectedness and according to which events are assessed for regulatory safety reporting to regulatory authorities.

"**Regulatory Application**" or "**RA**" means an IND-equivalent, non-U.S. Regulatory Application, applicable when the Clinical Trial is being conducted in whole or in part at a non-U.S. clinical research site.

"Samples" shall mean blood and/or blood derivatives collected from Human Subjects during the Clinical Trial.

"**Serious Adverse Event**" or "**SAE**" means the definition as stated in the Protocol.

"**Sponsor**" means, in accordance with the definition in 21 C.F.R. § 312.3, an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with Study Product. Daniel K. Benjamin, M.D., M.P.H., Ph.D. is the Sponsor and IND holder, and Syneos is the RA holder. Dr. Benjamin is the sponsor of record for this Agreement. Additionally, in accordance with 21 C.F.R. § 312.52(a) and any applicable HA requirements, several sponsor responsibilities will be transferred to TRI and its subcontractors, DCRI and Syneos. TRI is the ex-US Sponsor.

"**Statistical and Data Management Center**" or "**SDMC**" means the data management centers at TRI and DCRI responsible for providing statistical and data management services for ACTIV-IM.

"**Study Product**" means, in accordance with 21 C.F.R. § 50.3(j), any drug (including a biological product), medical device, food additive, color additive, electronic product, material, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301, *et seq*., Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended. In this Agreement Remicade® is referred to as the Study Product.

"**Technical Resources International Inc**" **or** "**TRI**" and their subcontractors, "Duke Clinical Research Institute" or "DCRI" and "Syneos Health" or "Syneos" means the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory, safety, data management and other activities for this clinical trial. TRI operates pursuant to a statement of work contained within an Award between BARDA and TRI. BARDA has named NCATS as its designee in the management of the statement of work in the awarded contract with TRI.

2. CLINICAL RESEARCH SITES AND INVESTIGATORS

2.1 Company will not provide any funding or material for any aspect of the Clinical Trial to any Clinical Research Site participating in the Clinical Trial without prior written notification to NCATS. In addition, subject to Section 14.4 of this Agreement, Company will not enter into any separate conflicting agreements pertaining directly to this Clinical Trial with the Clinical Research Sites and involving the Study Product. For the removal of doubt nothing in this clause shall prevent Company from entering into any agreement that is necessary to give effect to the conduct of this Clinical Trial, including, but not limited to, material transfer agreements, with the Clinical Research Sites or the Investigators at the Clinical Research Sites.

2.3 NCATS hereby certifies that it did not and will not utilize:

2.3.1 Any organization performing services in connection with this Clinical Trial that has been:

(i) debarred under the provisions of the Generic Drug Enforcement Act of 1992, 21 U.S.C. § 335a(a) and (b); or

(ii) suspended by OHRP as a clinical research site under 45 C.F.R. Part 46.

2.3.2 Any person convicted of a felony under federal law for conduct:

(i) relating to the development or approval, including, but not limited to, the process for development or approval, of any drug, product, medical device, New Drug Application (NDA), Biologics License Application (BLA), Pre-Market Application (PMA), 510(k) or IND or similar application; or

(ii) otherwise relating to the regulation of any drug product or medical device under the FDCA.

2.3.3 Any person performing services in connection with this Clinical Trial who has been disqualified as a clinical investigator under 21 C.F.R. § 312.70.

2.3.4 Any Investigator who is not qualified by training and experience as an appropriate expert to conduct the Clinical Trial, as required by 21 C.F.R. § 312.53. If either Party becomes aware that any organization or person involved in the Clinical Trial is debarred, threatened with debarment, disqualified, threatened with disqualification, or suspended, that Party will notify the other Party without any undue delay.

2.4 The Awards require that the Investigators at Clinical Research Sites conduct the Clinical Trial in accordance with applicable provisions of ICH E6: FDA/HA Good Clinical Practice Guidelines, and require that they comply with all applicable U.S., foreign government, state and local laws, regulations and guidelines.

2.5 Company agrees that this Protocol will be conducted only at sites selected and qualified by TRI and its subcontractors under the direction of NCATS. However, Company can conduct, at its own expense and under its own IND, additional clinical trials with the Study Product, at sites not participating in ACTIV-1 IM Trial. Company agrees not to knowingly impact the recruiting for the ACTIV-1 IM Trial. The Parties acknowledge that certain Affiliates or designees of NCATS, including but not limited to the consortium of sites, TRI and its subcontractors, DRCI and Syneos, the Investigators, Sponsor ('Designees') may be subject to obligations under this Agreement, by a delegation arrangement and/or by virtue of the Applicable Law. NCATS shall require that all the consortium of sites and TRI, and their sub-contractors DCRI and Syneos, the Investigator, Sponsor and its Affiliates shall conduct the Clinical Trial in accordance with the terms of this Agreement and with Applicable Law. NCATS shall procure the performance of this Agreement by such Designee that is involved in any manner in connection with the Clinical Trial in any part of the world. NCATS accepts liability for

its actions or the actions of its Affiliates or Designees with respect to this Agreement only to the extent permissible under Federal Law including but not limited to the Federal Tort Claims Act, 28 U.S.C. Chapter 171, et seq. and the Anti-Deficiency Act, 31 U.S.C. §1341, et seq.

3. INVESTIGATIONAL NEW DRUG APPLICATION SPONSORSHIP

3.1 **IND/RA.** (b)(6) , will be responsible for the submission of an IND covering the Protocol to the FDA, NCATS through DCRI will be responsible for the filing of subsequent IND submissions, and NCATS through Syneos will be responsible for the submission of any necessary RA. The IND/RA will satisfy all of the requirements of the FDA/HA, and, as applicable. Company will provide a letter granting the FDA/HA permission to cross-reference Company's pertinent Master File (MF), and/or IND/RAs in support of the Sponsor's IND/Syneos' RA, and in return, Sponsor and Syneos will also provide a letter to Company or its Affiliates as appropriate, if requested, granting the FDA/HA permission to cross-reference the IND/RA filed by Sponsor and Syneos for this Clinical Trial. Company agrees to provide all requested documents to DCRI and Syneos in pdf format. DCRI will provide a copy of all IND submissions to Company at the time they are submitted to the FDA. Any Confidential Information of another party will be removed.

3.2 NCATS through its relationship with TRI may delegate regulatory obligations to one or more third parties to facilitate NCATS's oversight, monitoring, and administration of the Clinical Trial at Clinical Research Sites outside of the United States provided that any and all delegates are subject to confidentiality requirements in relation to Company Confidential Information that is as stringent to the provisions set out in Section 13. NCATS 's third party delegate(s) will submit any clinical trial application and subsequent reports to all applicable HAs outside of the United States.

3.3 **Clinical Research Site Monitoring.**

3.3.1 TRI or their designee, will be responsible for Clinical Research Site monitoring in accordance with the clinical monitoring plan. Monitoring will be done in compliance with applicable provisions of the FDA/HA Good Clinical Practice Guidelines (ICH) (E6). TRI or its designee will communicate any Critical Event findings from clinical monitors to NCATS and Company within three (3) business days from TRI or its designee identifying a Critical Event finding . NCATS shall procure TRI's or its designee's, as applicable, performance with this Clause 3.3.

3.4 Adverse Event Reporting. Whilst NCATs has overall responsibility for Adverse Event reporting, NCATS sub-contracts the following Adverse Event reporting activities to TRI:

3.4.1 TRI will collect Adverse Event reports according to the procedure outlined in the Protocol and in timeframes consistent with 21 C.F.R. § 312.32 and Applicable Law where the Clinical Trial is being conducted in whole or in part at a non-U.S.

Clinical Research Site. The Clinical Research Sites will report Adverse Events to database in a timely manner and in accordance with the Protocol and Protocol Instruction Manual. TRI or their subcontractors will assume responsibility for the reporting of Adverse Events to the FDA/HA and will provide copies of all of the IND safety reports to Company.

3.4.2 TRI will report all unexpected Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the FDA/HAs and Company on a timely basis consistent with 21 C.F.R. § 312.32, Applicable Law where the Clinical Trial is being conducted in whole or in part at a non-U.S. Clinical Research Site and the Protocol. TRI will report other serious and non-serious adverse events to the FDA/HAs and to Company on a timely basis consistent with 21 C.F.R. § 312.33 and Applicable Law where the Clinical Trial is being conducted in whole or in part at a non-U.S. Clinical Research Site. TRI will report all Serious Adverse Events ("SAEs") associated with the Study Product observed in this Clinical Trial to the Company at the Safety Reports Address listed in the Contacts section within fifteen (15) days of awareness. TRI will report pregnancies with respect to Study Product to Company in a line listing on a monthly basis. Company agrees not to contact the Clinical Research Sites directly for information related to Adverse Events. Company shall contact the TRI Safety Office for information related to SAEs.

3.4.3 As the manufacturer, Company will, in a timely manner consistent with FDA/HA requirements and during the term of this Clinical Trial, provide TRI safety and/or the toxicity of the Study Product or any other Study Product information reasonably likely to impact the conduct of the Clinical Trial. TRI or its subcontractors will promptly transmit that information to all Investigators. Such information shall be sent to:

TRISafetyOffice@tech-res.com

3.4.4 During the course of the Clinical Trial, safety reports not meeting SUSAR criteria will not be unblinded. In the event that Company is requested by the FDA and/or a Health Authority to unblind a safety report, this request will be referred to NCATS and TRI, who hold the randomization codes and will consult with Company to determine whether the report can be unblinded without undermining the scientific integrity of the Clinical Trial. If there are concerns about patient safety, this will outweigh the risk of unblinding to scientific integrity of the Clinical Trial and the safety report must be unblinded. If it is determined that the safety report must be unblinded, NCATS shall, and if applicable shall procure that TRI or its subcontractors shall, be required to provide unblinded information to Company within twenty (24) hours of the request from Company to enable Company to meet the regulatory agency request. If it is determined that the safety report cannot be unblinded without undermining the scientific integrity of

the Clinical Trial, and there are no concerns about patient safety that outweigh the risk to the scientific integrity associated with unblinding, then NCATS shall, and if applicable shall procure that TRI or its subcontractors shall, collaborate with Company, as necessary, in providing a timely response to the FDA/Health Authority. During the course of the Clinical Trial, if NCATS / TRI / Syneos is requested by FDA and/or a Health Authority to unblind a safety report (a similar assessment will take place regarding the scientific integrity upon unblinding) they will inform the Company and proceed with providing the required information or justification for not unblinding. NCATS and TRI reserve the right to unblind a SUSAR report without consulting with Company if concerns about patient safety are generally thought to outweigh the risk to scientific integrity and will promptly inform the Company of the unblinding.

4. SAFETY MONITORING

Data and Safety Monitoring Board (DSMB). The NIAID DSMB will monitor this Clinical Trial as described in the Protocol and inform NCATS of its recommendations. NCATS will notify Company in advance of any DSMB review. NCATS will provide recommendations derived from the DSMB to Company within a reasonable period of time.

5. FDA/HA MEETINGS/COMMUNICATIONS

5.1 With respect to any discussions with the FDA/HA involving data obtained from this Clinical Trial under the Sponsor's IND or the Syneos RA, DCRI or Syneos, in consultation with Company, will take the initiative in arranging meetings or conference calls with the FDA/HA. Formal meetings with the FDA/HA concerning the Clinical Trial design and/or data, as well as formal responses to any FDA/HA questions and requests for information, will be discussed and agreed upon in advance by Company and NCATS, TRI, DCRI and Syneos. Company will have the right to participate in all formal meetings with the FDA/HA regarding the Study Product. Company agrees not to contact the FDA/HA independently of NCATS, DCRI or Syneos concerning this Clinical Trial. However, Company may contact the FDA/HA on separate product-related issues. DCRI will provide Company with copies of all transmittal letters and other formal communications for IND submissions, and formal questions and responses that have been submitted to and received from the FDA. TRI and/or its designees will verify through clinical site monitoring that RA submissions were submitted to the relevant HA according to applicable laws, rules, regulations and guidelines. Any Confidential Information of another party will be removed.

5.2 Company will promptly notify NCATS of:

(a) Any FDA/HA correspondence related to the Protocol that is received by Company, or its Affiliates; and

(b) FDA/HA enforcement actions directed toward Company or its Affiliates, including, but not limited to, warning letters, seizures, or recalls; injunctions/consent decrees; rejection of regulatory submissions or withdrawal of approval as it pertains to the Study Product;

5.3 Company will also promptly notify NCATS of any action taken by the FDA/HA regarding manufacturing of the Study Product that would impact the safety of Human Subjects in the Clinical Trial.

6. SUPPLY, DISTRIBUTION AND USE OF STUDY PRODUCT

6.1 **Supply.** NCATS shall provide Company with an estimate of the quantity of Study Product as set in Appendix 1 that will be required to complete the Protocol. Without the need for further written Amendments, NCATS and its contractor shall have the flexilibity to move quantities around the various sites. Company will supply the Study Product to NCATS without charge and in quantities and conditions sufficient to complete the Protocol and on a schedule mutually agreed upon by the Parties to ensure a sufficient supply of unexpired Study Product subject to ongoing review and discussion between the Parties. Company will be responsible for labeling the Study Product used in the Clinical Trial. Company and TRI or its designee have entered into a quality agreement in respect of the Study Product which said agreement is attached hereto as Appendix 2.

6.2 **Distribution.**

6.2.1 Company will ship the Study Product to a central distribution site(s) to be arranged by TRI and communicated to the Company. Company will provide specific storage and/or shipping instructions for the Study Product to TRI on behalf of NCATS, its designee, the central distribution site(s), and/or the Clinical Research Sites, who will be responsible for adhering to them, as mutually agreed by the Parties. Company warrants that any packaging for hazardous material, provided by Company, meets Department of Transportation regulatory requirements for use at all Clinical Research Sites.

6.2.2 The Study Product must be received by the central distribution site(s) or Clinical Research Sites in usable condition and accompanied by Material Safety Data Sheet (MSDS), specific storage and shipping instructions, stability and/or expiration dating information, Certificate of Analysis (CoA) and the Certificate of Compliance (CoC).

6.2.3 If there is evidence that the Study Product that arrived at the central distribution site(s) or Clinical Research Sites has not been maintained according to the defined shipping instructions, or is potentially adulterated, NCATS will contact Company to inform it of the condition of the received Study Product and to determine if the Study Product is usable or if it must be replaced. If the Study Product must be

replaced, Company will replace it at no cost to NCATS , the central distribution site(s), or the Clinical Research Sites.

6.3 **Use.** NCATS will not transfer the Study Product to parties other than the central distribution site(s) or the Clinical Research Sites, nor will NCATS chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed in writing by the Parties. NCATS, pursuant to the Awards, will ensure that the Investigators: (i) use the Study Product only in accordance with the Protocol and for no other purpose; (ii) do not transfer the Study Product to any parties except Company, the central distribution site(s), or the Clinical Research Sites; and (iii) do not chemically modify, replicate, make derivatives of, or reverse engineer the Study Product unless mutually agreed to, in writing, by the Parties. NCATS shall ensure on their own behalf and on behalf of their designee that they store the Study Product in accordance with the Investigational Product Preparation Instruction (IPPI) and the Quality Agreement.

6.4 **Study Product Return.** Upon completion of the Protocol, NCATS will ensure destruction or, at Company's request, return any unused Study Product to Company.

6.5 **Warranty.** Company represents and warrants that the Study Product supplied meets the specifications cited in the CoA and CoC provided.

6.6 **Source.**

6.6.1 In the event Company elects to terminate its development of Study Product for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to NCATS within ninety (90) days of discontinuation then Company will provide NCATS with Study Product sufficient to complete the Clinical Trial in the manner described in the Protocol.

6.6.2 The Parties also agree that should this Agreement be terminated prior to completion of the Protocol, the Protocol will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol and Company will supply enough Study Product to complete the Protocol.

7. INVESTIGATOR'S BROCHURE (IB)

7.1 Company will provide a current IB in eCTD format for all applicable components of the Study Product, and any later revisions and addenda to the IB for the Study Product, including a summary of changes (SOC), to NCATS, or to TRI or its subcontractors, as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Section 13 (Confidential Information) of this Agreement. Company agrees to provide NCATS, or to TRI or its subcontractors, as mutually agreed by the Parties, any updated version of the IB, with the SOC, within fifteen (15) days of issuance. Company will send the IB and SOC to the NCATS to the attention of the NCATS contact for

regulatory matters identified in Article 26, or to NCATS' designee. NCATS through TRI or its subcontractors, will distribute the IB to the Clinical Research Sites. NCATS or TRI or its subcontractors, will address requests for IBs, including updated versions and SOCs, to:

(b)(6)
(b)(6)
Janssen Biotech Inc
800/850 Ridgeview Drive,
Horsham PA 19044, United States of America
Phone: (b)(6)
E-mail: (b)(6) @its.jnj.com

7.2 The IB shall serve as the Reference Safety Information in respect of the Study Product for the Clinical Trial and shall serve as a reference for any expectedness assessment of adverse events by TRI on the basis of the IB.

8. PROTOCOL DEVELOPMENT AND REGISTRATION

8.1 The Parties agree that enrollment in the Clinical Trial will not start until the version of the Protocol to be used has been reviewed in advance by Company, accepted by the Protocol Team, approved by the relevant IRB(s)/IEC(s) and NCATS in writing, submitted to the FDA/HA, and any clinical hold issues have been responded to satisfactorily.

8.2 The Parties agree that any alteration in or amendment to the Protocol must be accepted by the Protocol Team, approved in writing by the relevant IRB(s)/IEC(s) and NCATS, and submitted to the FDA/HA prior to such alteration or amendment becoming effective.

8.3 The Parties acknowledge that all NIH protocols will be registered and maintained on ClinicalTrials.gov by TRI or its subcontractor, consistent with the NIH policy Requirements for Registering & Reporting NIH-funded Clinical Trials in ClinicalTrials.gov and that the informed consent must meet all federal mandates to ensure the welfare of Human Subjects in the Clinical Trial.

9. DEVELOPMENT OF CASE REPORT FORM AND STATISTICAL ANALYSIS PLAN

TRI and DCRI, through the SDMC, will be responsible for the development and subsequent revisions, if any, of the Case Report Forms and Statistical Analysis Plan with appropriate review and comment by the Protocol Team.

10. HUMAN SUBJECTS PROTECTION

10.1 NCATS and Company recognize the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report and will apply these principles in all research covered under this Agreement. The informed consent of each Human Subject participating in the Clinical Trial at a Clinical Research Site will be obtained prospectively using an informed consent process. The sample informed consent document may be reviewed in advance by Company and shall be approved by NCATS and all appropriate IRB(s)/IEC(s).

10.2 NCATS and Company acknowledge and accept their responsibilities for protecting the rights and welfare of Human Subjects set forth in 45 C.F.R. Part 46, Protection of Human Subjects. Therefore:

10.2.1 NCATS and Company will maintain the confidentiality of IPI shared between them in accordance with the Protocol, including PHI, collected under the Clinical Trial and protect the privacy of the individual Human Subjects unless disclosure is required by law.

10.2.2 To the extent permitted by the informed consent forms and applicable laws, TRI and Company may inspect, but not copy, Human Subjects' medical records that might also include information not directly connected to this Clinical Trial. However, TRI and Company agree that this information will remain confidential and will not be used for any purpose other than confirmation of Clinical Trial data or to resolve study-related injury issues.

10.2.3 NCATS and Company agree that neither Party will use, nor will it allow its contractors to use, IPI for any purpose not stated in the Protocol, without the consent of the other Party and local site IRB/IEC approval unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative. NCATS will ensure that the Investigators do not use IPI for any purpose not stated in the Protocol and informed consent document without the written consent of both Parties and appropriate IRB/IEC approval, unless such purpose is related to the resolution of study-related injury issues at the request of the Human Subject or his/her legal representative.

10.2.4 NCATS and Company agree to comply with the determinations of all IRB(s)/IEC(s) overseeing this research.

10.2.5 Biospecimens and data related to biospecimens provided to Company during and after the Clinical Trial, if any, will be coded.

10.3 <u>Testing of Samples by Company</u>

10.3.1 As part of the Protocol, Samples may be transferred to Company or its Affiliate only if this is arranged for in the ICF. If there are no samples, then NCATS has no obligation to send them to Company. NCATS has no obligation to provide storage facilities.

10.3.2 Company or its Affiliate shall have the right to store, transfer and use the Samples only in accordance with the applicable Law, the Protocol and ICF (as approved by the Ethics Committee). NCATS shall promptly notify Company or its Affiliate of any withdrawal of or changes in the informed consent of a Clinical Trial Subject, which may affect the use of such Clinical Trial Subject's Samples under this Agreement. In such event, Company or its Affiliate shall destroy or return the affected Samples if necessary.

10.3.3 Upon termination or expiration of the Clinical Trial, and at least at any time the Samples are no longer needed to be retained by Company or its Affiliate for any pending registration purpose related to the Study Product in relation to the Protocol or as defined in the ICF, or as required per any Applicable Law or regulation, the remainder of the Samples in Company's or any of its Affiliates' possession will be returned to the Clinical Sites, or destroyed by the Company or its Affiliate, as described in the Protocol and/or the ICF.

10.3.4 For the avoidance of any doubt, the control of the Samples remains at all times at the Clinical Trial Subjects they are derived from, with the NCATS and/or Company or its Affiliate acting as custodian of the Samples, as described in the Protocol.

10.3.5 In accordance with Section 1.1.8 Schedules of Assessment Table 1.1 of the Protocol Company reserves the right to request and receive and test further Samples from NCATS and/or the Clinical Sites at Company's sole cost and expense for securing and shipment. NCATS will only provide Company with Samples that were obtained during the Clinical Trial. Furthermore, NCATS will not be responsible for long term storage of the Samples after the completion of the Clinical Trial.

11. DATA COLLECTION, ANALYSIS AND MANAGEMENT

11.1 The Clinical Research Sites will be responsible for gathering all data arising from the Clinical Trial and submitting it to TRI/DCRI. The Protocol Team, which includes Company representatives, will be responsible for the scientific reporting of the data as provided for in Section 12 of this AgreementIf requested by IRBs, FDA or HAs, the Protocol Team will provide study enrollment or progress updates, if needed.

11.2 TRI, through the SDMC, will have responsibility for the data management: collection, entry and quality control edits (with implied verifications and documentation) and analysis of data obtained from the Clinical Trial in accordance with the Protocol.

11.3 It is the responsibility of both Company and NCATS to protect the scientific integrity of the ACTIV-1 IM study. Doing so requires maintaining the study blind throughout the ACTIV-1 IM protocol. Access to unblinded data during the protocol will be made available only to the DSMB, unblinded statisticians and unblinded CRAs and subject to

Clause 3.4.4 may be made available to Company. Based on predefined guidance in the statistical analysis plan (SAP), the DSMB will make a determination if the Study Product can continue. If the Study Product does not proceed, the data will be made available to Company, in the form of Study Data Tabulation Model (SDTM) datasets, only after placebo data from the Company substudy has been used to analyze all other concucrrent substudies. The Protocol Team will remain blinded throughout.

All data obtained from the Clinical Trial will be in the custody of the Investigator or the Clinical Research Site, as applicable, which produces such data. However, other than Company, its contractors and its designees, any party wanting to review or use the data obtained from the Clinical Trial for purposes of seeking regulatory approval of the Study Product or otherwise will obtain the prior written permission of Company.

11.4 Upon completion of the data analyses for the Study Product, NCATS will authorize the SDMC to transfer to the Company a copy of the clinical database (SDTM format) and data analysis set(s) (ADaM format) and results of statistical analysis of the infliximab (remicade) Sub-Study related to the Study Product and matched control in a machine-readable format to be determined jointly by the Parties. If Company requires that the data be provided in a customized format(s), Company will pay for all costs associated with the customized data format(s).

11.5 Subject to the right of NCATS and the Investigators to publish the data from this Clinical Trial as set forth in the Publications and Press Releases Section of this Agreement, Company has the right to utilize the data reports from this Clinical Trial in its possession for all legitimate business or regulatory purposes. NCATS and/or Company may provide any information regarding the Clinical Trial to governmental organizations including, but not limited to, the FDA/HA and the Securities and Exchange Commission (SEC), for all legitimate public health, regulatory or business purposes. Except for information related to regulatory or safety issues or under emergency circumstances where it is not practicable to do so and to the extent permitted by law, NCATS will not release information regarding the Clinical Trial to governmental organizations without prior notification to Company.

11.7 NCATS, through TRI, will be responsible for preparing and submitting the final Clinical Study Report in accordance with ICH E3, "Structure and Content of Clinical Study Reports." NCATS shall procure or shall procure that TRI shall provide Company with a copy of the final Clinical Study Report as soon as possible but within six (6) months from database lock for the Clinical Trial.

12. PUBLICATIONS AND PRESS RELEASES

12.1 The Parties acknowledge that results of the Clinical Trial will be disseminated in accordance with the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information. The expectation of the policy is that all NIH-funded awardees and investigators conducting clinical trials will register and report results of their trial in Clinicaltrials.gov. Unless requested otherwise by Company, NCATS Protocol Team will

acknowledge Company as the source of the Study Product in any NCATS publication resulting from the Clinical Trial and will ensure that the Investigators do the same in their publications resulting from the Clinical Trial. For the removal of doubt Company shall have the right to publish and disseminate the results of the Clinical Trial.

12.2 Recognizing that employees of either Party may play an important role in the design, analysis and interpretation of the findings of the Clinical Trial, each Party will include appropriate individuals from the other Party in the authorship of publications resulting from the Clinical Trial, in accordance with the generally accepted customs pertaining to authorship and meeting those set out in the International Committee of Medical Journal Editors. NCATS will ensure that the Investigators include appropriate individuals from both Parties in their publications resulting from the Clinical Trial.

12.3 Each Party will provide, and NCATS will ensure that the Investigators provide, a copy of any abstract or manuscript to the other Party prior to submission for publication with sufficient time for review and comment: thirty (30) days for manuscripts and fourteen (14) days for posters and abstracts. The publication or other disclosure may be delayed for up to thirty (30) additional business days for manuscripts and up to five (5) business days for abstracts, upon written request by either Party as necessary to preserve U.S. or foreign Patent or other intellectual property rights. If identified by Company, all Confidential Information belonging to Company that may be contained in any publication or public disclosure shall be deleted. Company will cooperate with NCATS to provide alternate information for such Confidential Information if such alternate information exists at Company's reasonable discretion. Each Party agrees that, following the receiving Party's review of the manuscript and/or abstract for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish, present or use any Clinical Trial data. Notwithstanding the timelines described above, the Parties agree that expedient publication of the Clinical Trial results is necessary for the public good and the Parties agree to work in good faith to allow expeditious publication of the Clinical Trial results.

12.4 Each Party will provide, and NCATS will ensure that the Investigators provide, a copy of any proposed press release to the other Party for review and comment not less than ten (10) business days in advance of proposed publication. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum periods of time specified above, the submitting Party and/or the Investigators will be free to publish the press release.

13. CONFIDENTIAL INFORMATION

13.1 Either Party may disclose and/or receive Confidential Information under the terms and conditions of this Agreement. Each receiving Party will limit its disclosure and use of the disclosing Party's Confidential Information to the amount necessary to conduct the Clinical Trial. The disclosing Party will place a confidentiality notice on all the Confidential Information. The disclosing Party will reduce confidential non-written communications to writing within thirty (30) business days of first disclosure. Each Party

receiving Confidential Information agrees that any information so designated will be used by it only for the purposes of the Clinical Trial. Any Party may object to the designation of information as Confidential by the other Party and /or to correct any document where Confidential Information is omitted.

13.2 Unless expressly provided otherwise, neither Party will disclose, copy, reproduce or otherwise make the disclosing Party's Confidential Information available to any other person or entity without the consent of the disclosing Party unless required by a court or administrative body of competent jurisdiction, the Freedom of Information Act (FOIA), 5 U.S.C. § 552, or other applicable laws and/or regulations to disclose the Confidential Information, except that NCATS and Company may disclose Confidential Information to those of their representatives, agents, officers, grantees, contractors, consultants and employees (collectively, "Agents") to the degree necessary to conduct the Clinical Trial. NCATS hereby represents that its respective Agents including but not limited to TRI and its subcontractors and the Study Sites shall maintain the confidentiality of Confidential Information in accordance with the terms of this Agreement. .and shall be subject to a written confidentiality agreement containing obligations of confidentiality no less stringent than those set out herein.

13.3 Each Party will use the same level of care it uses with its own Confidential Information, but no less than a reasonable level of care, in maintaining the confidentiality of the other Party's Confidential Information. Current NIH policy requires that a brief synopsis, the enrollment status and study results for all NIH-funded clinical trials be posted in the ClinicalTrials.gov registry of clinical studies, available through the NIH website. TRI shall be responsible for submitting information to ClinicalTrials.gov.

13.4 Each Party agrees that the receiving Party is not liable for the disclosure of Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given an opportunity to seek a court order to enjoin from disclosure.

13.5 Each Party's obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined above, or five (5)after the expiration or termination date of this Agreement. Either Party may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

14. INTELLECTUAL PROPERTY

14.1 Ownership of any Iinvention made solely or jointly by NCATS, the Clinical Research Sites and Investigators, or other NCATS contractors or grantees as a consequence of conducting the Clinical Trial and involving the Study Product, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party claims by virtue of this Agreement any right, title, or interest in or to any issued Patents or pending Patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement

will be construed as granting any license or obligation to license any intellectual property owned by Company to NCATS with respect to the Study Product, other than the limited right to use the Study Product for the performance of the Protocol in accordance with the terms of this Agreement. Any inventions, originating, conceived, discovered and/or reduced to practice during the performance of Research under this Agreement under this Agreement (individually and collectively, "Inventions") and any patents filed on such Inventions shall be determined under U.S. patent law in accordance with inventorship.

14.2 **NCATS Intellectual Property.**

14.2.1 The Government will retain title to any Patent or other intellectual property rights in inventions made solely by NCATS employees in the course of the Clinical Trial.

14.2.2 NCATS agrees to notify Company of any such Invention relating to Study Product and is willing to disclose it to Company only under an appropriate confidentiality agreement. Company may apply for exclusive license rights to any patentable Invention made by NCATS employees that might arise during the clinical research and the NIH will consider Company's application for a license consistent with 37 C.F.R. Part 404. NCATS agrees to grant Company a non-exclusive license consistent with 37 C.F.R. 404, for NCATS owned Inventions that relate to the Study Product.

14.3 **Company Intellectual Property.** Company will retain title to any Patent or other intellectual property rights in Inventions made solely by its employees during the course of the Clinical Trial.

14.4 **Clinical Research Site/Investigator Intellectual Property.** This Agreement does not grant or preclude intellectual property rights, including, but not limited to, Inventions made by TRI, the Investigators, or other Government contractors or grantees during the course of the Clinical Trial. Company may enter into a separate agreement with the Clinical Research Sites or Investigators regarding intellectual property rights that do not interfere with the conduct of this Clinical Trial or contradict the terms of this Agreement.

14.5.1 **Joint NCATS -Company Intellectual Property.** NCATS and Company will have joint intellectual property rights in Inventions made jointly by their employees during the course of the Clinical Trial.

14.5.2 For any Inventions to which Company and NCATS have joint ownership, Company may elect to file and prosecute at its expense a patent application in the name of Company and NCATS on the Inventions described in such disclosure; however, NCATS may itself file and prosecute at its expense any patent application on behalf of NCATS and Company on such Inventions should Company elect not to do so within a reasonable time after such invention disclosure.

14.5.3 With respect to all patent applications prepared and/or prosecuted by NCATS claiming any Inventions in which Company has rights, at Company's request, NCATS shall

provide Company with electronic copies of all prosecution, and a reasonable opportunity for Company to provide comments to NCATS on pending prosecution.

15. FORCE MAJEURE

Neither Party will be liable for any unforeseeable event beyond its reasonable control not caused by the fault or negligence of such Party, which causes such Party to be unable to perform its obligations under this Agreement, and which it has been unable to overcome by the exercise of due diligence. In the event of the occurrence of such a force majeure event, the Party unable to perform will promptly notify the other Party. It will further use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the force majeure event.

16. LIABILITY, INDEMNIFICATION AND INSURANCE

16.1 **Liability.** Activities carried out under this Agreement are covered under the Public Readiness and Emergency Preparedness Act (PREP Act) as implemented under the amended declaration, "Public Readiness and Emergency Preparedness Act Coverage for medical countermeasures against COVID–19," issued on March 17, 2020 (85 Federal Register 15198). The PREP Act provides immunity from liability claims against manufacturers, distributors, program planners and other qualified persons ("Covered Persons") arising from the administration and use of covered countermeasures, as specified in a declaration by the Secretary of HHS ("Secretary") [See section 319F-3 of the Public Health Service Act (42 U.S.C. §247d-6d)]. The exception to this immunity is acts of willful misconduct by the Covered Persons. The Study Product is considered a drug to treat, prevent or mitigate COVID-19, and as such is a covered countermeasure under the Secretary's declaration. Informed consent forms used in the Clinical Trial will include a sufficient description of the PREP Act for participants to understand that all Covered Persons have immunity from liability under the PREP Act, and what compensation may be available under the PREP Act Countermeasure Injury Compensation Program [See section 319F-4 of the Public Health Service Act (42 U.S.C. §247d-6e)]. To the extent that PREP Act coverage is not available, each Party shall be liable for any loss, claim, damage or liability that it incurs as a result of its direct activities under this Agreement, except that NCATS, as an agency of the U.S. Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Ch. 171.

16.2 **Indemnification.** NCATS is prohibited under the Anti-Deficiency Act, 31 U.S.C. § 1341 from indemnifying Company for any losses incurred as a result of this Clinical Trial. Each Party will be liable for the losses, claims, damages or liabilities that it incurs as a result of its activities under this Agreement. Company's right and obligation to defend NCATS and Company's control over the defense and settlement of any claim against NCATS will be subject to the consent of NCATS and the Department of Justice.

To the extent that PREP Act coverage is not available, Company will defend, indemnify and hold harmless the Government's grantees and contractors and their respective agents and employees ["Indemnitee(s)"] from any and all liabilities, damages, losses, claims, action, suits and expenses, including attorneys' fees and court costs (collectively "Claims") to the extent caused by the proper administration or use of the Study Product during the course of the Clinical Trial, provided, however, that Company's obligation to so indemnify Indemnitee(s) will only apply if each of the following conditions is met:

16.2.1 The Claim was not proximately caused by the Indemnitee(s)' failure to conduct the Clinical Trial in accordance with the Protocol, any written instructions from Company, and this Agreement.

16.2.2 The Claim was not caused by the negligence, recklessness or willful misconduct of any Indemnitee, provided that any action properly taken by the Indemnitee in compliance with the Protocol or written instructions from Company will be deemed, for purposes of this condition, not to be negligent, and provided further that if a Claim is jointly caused by the negligence of any Indemnitee and the administration or use of the Study Product, then Company will provide defense and indemnification to the extent the Claim was caused by the administration of the Study Product.

16.2.3 Company is promptly notified of the Claim, provided that the failure to give such notice will not abrogate or diminish Company's defense and indemnity obligation if Company has or receives knowledge of the existence of the Claim by any other means or if such failure does not prejudice Company's ability to defend the Claim.

16.2.4 Company will have sole control over the defense and settlement of the Claim(s) directed against the Company.

16.2.5 Company will have the right to select defense counsel and to direct the defense and settlement of the Claim(s) directed against the Company.

16.2.6 Company will provide a diligent defense against and/or settlement of any Claims for which defense and indemnification are provided under this Agreement whether such Claims are rightfully or wrongfully made. Company will have the right to settle such Claims, at Company's sole expense and in Company's sole discretion. Indemnitee(s) will fully cooperate, at Company's expense, with Company and its legal representatives in the investigation and defense of any Claim for which defense and indemnification are provided under this Agreement.

16.2.7 The Indemnitee(s) will at all times have the right to fully participate in the defense of any Claim at their own expense and for their own account. If Company will, within a reasonable time after notice, fail to defend any Claim for which defense and indemnification are provided under this Agreement, the Indemnitee(s) will have the right, but not the obligation, to undertake the defense of and to

compromise or settle the Claim on behalf, for the account, and at the risk of Company.

16.3 **Participant Injury Attributable to the Clinical Trial**. To the extent that PREP Act coverage is not available, Company will pay the reasonable cost of medical care required by Clinical Trial participants for illness or injury attributable to the Study Product. For purposes of this determination and Company's obligation under this Agreement, "attributable" means that the receipt of the Study Product and the Clinical Trial participant's illness or injury are reasonably related in time, and the illness or injury is more likely explained by the receipt of the Study Product than another cause.

The payment or offer of payment of any amount by Company on behalf of a participant or his or her healthcare insurer or other third party payer under this Section is not an admission of fault or liability by any one or more of (a) the United States Government or any agency thereof; (b) the Clinical Research Site or its affiliate organizations, or (c) Company, its employees or agents, and any such payment or offer of payment will not be considered a waiver of any defense or other legal right by any of the foregoing in any legal, administrative or similar proceeding.

16.4 **Insurance.** Company represents and warrants that it will maintain during the term of this Agreement or the Protocol, whichever is longer, a liability insurance policy or a program of insurance or self-insurance at levels sufficient to support the research related injury and indemnification obligations assumed under this Agreement. Upon request, Company will provide evidence of its insurance or self-insurance to NCATS.

17. DISPUTE RESOLUTION

Any dispute arising under this Agreement that is not disposed of by agreement of the Parties will be submitted jointly to the signatories of this Agreement. If the signatories are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the dispute will be referred to the Director of Division of Clinical Innovation, NCATS (or his/her designee) and an appropriate authorized representative of Company for resolution. If the Director of DCR (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute through good faith negotiations within thirty (30) days, the dispute will be referred to the Director of NCATS (or his/her designee) and the authorized representative of Company. If the Director of NCATS (or his/her designee) and the authorized representative of Company are unable to jointly resolve the dispute, either Party may pursue any and all administrative or judicial remedies that may be available.

18. INDEPENDENT CONTRACTORS

In the performance of all work under this Agreement, neither Party is authorized or empowered to act as agent for the other for any purpose and will not, on behalf of the other Party, enter into any contract, warranty, or representation as to any matter. Neither Party will be bound by the acts of the other Party.

19. NON-ENDORSEMENT

By entering into this Agreement, NCATS does not directly or indirectly endorse any product or service provided, or to be provided, by Company. Company will not in any way state or imply that this Agreement is an endorsement of those product(s) or service(s) by the Government or any of its organizational units or employees. However, Company may reference or use publications and reports based on the Clinical Trial for legitimate business and regulatory purposes.

20. AMENDMENTS

Modifications to this Agreement will not be effective unless made in writing, as mutually agreed, and signed by a duly authorized representative of each Party.

21. SURVIVABILITY

The provisions (Clinical Research Sites and Investigators), (Investigational New Drug Application Sponsorship), (Supply, Distribution and Use of Study Product), (Human Subjects Protection), (Data Collection, Analysis and Management), (Publications and Press Releases), (Confidential Information), (Intellectual Property), (Liability, Indemnification and Insurance), (Dispute Resolution), (Independent Contractors), (Non-Endorsement), (Amendments) and this Section (Survivability) will survive the expiration or earlier termination of this Agreement.

22. ENTIRE AGREEMENT AND SEVERABILITY

This Agreement constitutes the entire agreement and understanding of the Parties with respect to the subject matter hereof and supersedes any prior understanding or written or oral agreement. The provisions of this Agreement are severable and, in the event that any provision of this Agreement will be determined to be invalid or unenforceable under any controlling body of law, such determination will not in any way affect the validity and enforceability of the remaining provisions of this Agreement.

23. ASSIGNMENT AND SUBCONTRACTING

Neither this Agreement nor any rights or obligations of any Party hereunder will be assigned or otherwise transferred by either Party without prior written notification to the other Party. The terms and conditions of this Agreement shall be binding on and inure to the benefit of the permitted successors and assigns of the Parties.

The Parties agree that either Party is permitted to assign one or more sub-contractors to the whole or part of its performance under this Agreement but each Party shall remain fully responsible and liable for the performance of its obligations under this Agreement, regardless of any such sub-contracting. Each Party shall notify the other of any subcontractors engaged in accordance with this section.

24. APPLICABLE LAW

This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

25. TERM AND TERMINATION

Unless terminated sooner in accordance with this Term and Termination Section, this Agreement will expire upon completion of the Clinical Trial. The Parties may terminate this Agreement at any time by mutual written consent. Either Party may unilaterally terminate this Agreement at any time by giving written notice at least thirty (30) days prior to the desired termination date. The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial, the Clinical Trial will be completed if medically appropriate. In that event, each enrolled participant will be followed through the period outlined in the Protocol, and Company will supply enough Study Product to complete the Clinical Trial in accordance with Appendix 1. In the event that Company elects to terminate its obligations under the terms of this Agreement, due to an unexpected dissolution, Company must notify NCATS within at least thirty (30) days of the dissolution.

26. NOTICES

Any notice or report required under the terms of this Agreement will be sent to the other Party at the following addresses. Any notice will be deemed to be effective when delivered to the other Party by courier, registered mail (with return receipt) or via facsimile followed by confirmational hard copies sent via international courier when it is necessary to receive or deliver documents within a very short period of time [less than one (1) day].

For Company:

Legal Department
Janssen Biotech, Inc.
800/850 Ridgeview Drive, Horsham PA 19044, USA

For regulatory matters:

(b)(6)

Janssen Research & Development,
1400 McKean Road, Spring House, PA 19477, USA

For matters concerning Safety Reports:

As set out in Appendix 3

For NCATS :

(b)(6)
NCATS
National Institutes of Health
Department of Health and Human Services
6701 Democrcy Blvd, Suite 900
Besthesda, MD 20817
Phone: (b)(6)
Email (b)(6) @nih.gov

For Legal Notices:

(b)(6)
Director Office of Strategic Alliances
National Center for Advancing Translational Sciences, NIH
9800 Medical Center Drive, Room 340B
Rockville, MD 20850
Phone: (b)(6)
Email: (b)(6) @nih.gov

For regulatory matters:

(b)(6)
NCATS
National Institutes of Health
Department of Health and Human Services
6701 Democrcy Blvd, Suite 900
Besthesda, MD 20817
Phone: (b)(6)
Email: (b)(6) @nih.gov

27. COUNTERPARTS

This Agreement may be executed in counterparts, each of which shall be deemed an original, and all of which, taken together, shall constitute one and the same instrument. Signatures to this Agreement transmitted by fax, by electronic mail in portable document (.pdf) format, or by any other electronic means intended to preserve the original graphic and pictorial appearance of the Agreement, will have the same effect as physical delivery of the paper document bearing the original signature.

SIGNATURES BEGIN ON THE NEXT PAGE

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

For NCATS:

(b)(6)

Digitally signed by (b)(6)
Date: 2020.10.07 15:19:15 -04'00'

(Signature) (Date)

for (b)(6)
Deputy Director
National Center for Adavancing Transltional Sciences
National Institutes of Health
Department of Health and Human Services

For BARDA – Read and Acknowledged

(b)(6)

Digitally signed by (b)(6)
Date: 2020.10.08 08:36:51 -04'00'

(Signature) (Date)

(b)(6)
Director, Division or Clinical Development
BARDA

For Technical Resources International, Inc. – Read and Acknowledged

(b)(6)

Digitally signed by (b)(6)
Date: 2020.10.07 15:51:58 -04'00'

(Signature) (Date)

(b)(6) Director of Contracts
Technical Resources International, Inc.
6500 Rock Spring Drive, Suite 650
Bethesda, Maryland 20817

For Company:

(b)(6)

October 6, 2020

(Signature) (Date)

(b)(6)
Janssen Biotech, Inc.
800/850 Ridgeview Drive, Horsham PA 19044

cc: Principal Investigators, Clinical Research Sites

Appendix 1: Schedule of Provision of Remicade Vials for ACTIV-1 IM Study by Janssen

Country	**Target Ship date from Janssen**	**Quantity**
USA	~ Week of 14 September 2020 ~ Week of 12 October 2020	~ 2800 vials (Campaign 1) ~ 3000 vials (Campaign 2)
Argentina	~ Week of 12 October 2020	2000 vials
Brazil	~ Week of 12 October 2020	2000 vials
Peru	~ Week of 12 October 2020	2000 vials
Colombia	TBD – back up country	2000 vials

If any supplemental shipments are requested by NCATS outside of the above quantities to meet adjusted country enrollment targets, these shall be provided by Company.

Appendix 2: Quality Agreement

Appendix 3 – Contacts

For Company:

Safety Reports Address:

Adverse Event Reporting Mailbox GMS_AE_Inbo@its.jnj.com

For NCATS:

ACTIV-1SafetyReporting@nih.gov

For TRI:

TRISafetyOffice@tech-res.com

Appendix 4

ACTIV-1 Protocol Team Roster

Chair

NCATS Representatives

OWS Representative

BARDA Representative

Clinical TX WG/NIAID Representative

Statisticians – Blinded/Unblinded

Site Investigator Representative (domestic and international)

Site Coordinator Representative

Community Representative – Chair of Community Advisory Board

U.S. IND Sponsor

EX-U.S. HA Sponsor

Industry Representatives – 1-2 per company

FNIH Representative

Study Pharmacy Representative

Coordinating Center Representative (s)

V 1.0 21 Sep 2020



QUALITY AGREEMENT

BETWEEN

Technical Resources International, Inc.

6500 Rock Spring Drive, Suite 650

Bethesda, Maryland 20817

(Hereinafter referred to as "INSTITUTION")

and

Janssen Research & Development, Division of Janssen Pharmaceutica NV, and affiliates
Turnhoutseweg 30,
2340 Beerse, Belgium
Use Janssen Name as in Overarching agreement
(Hereinafter referred to as "COMPANY")

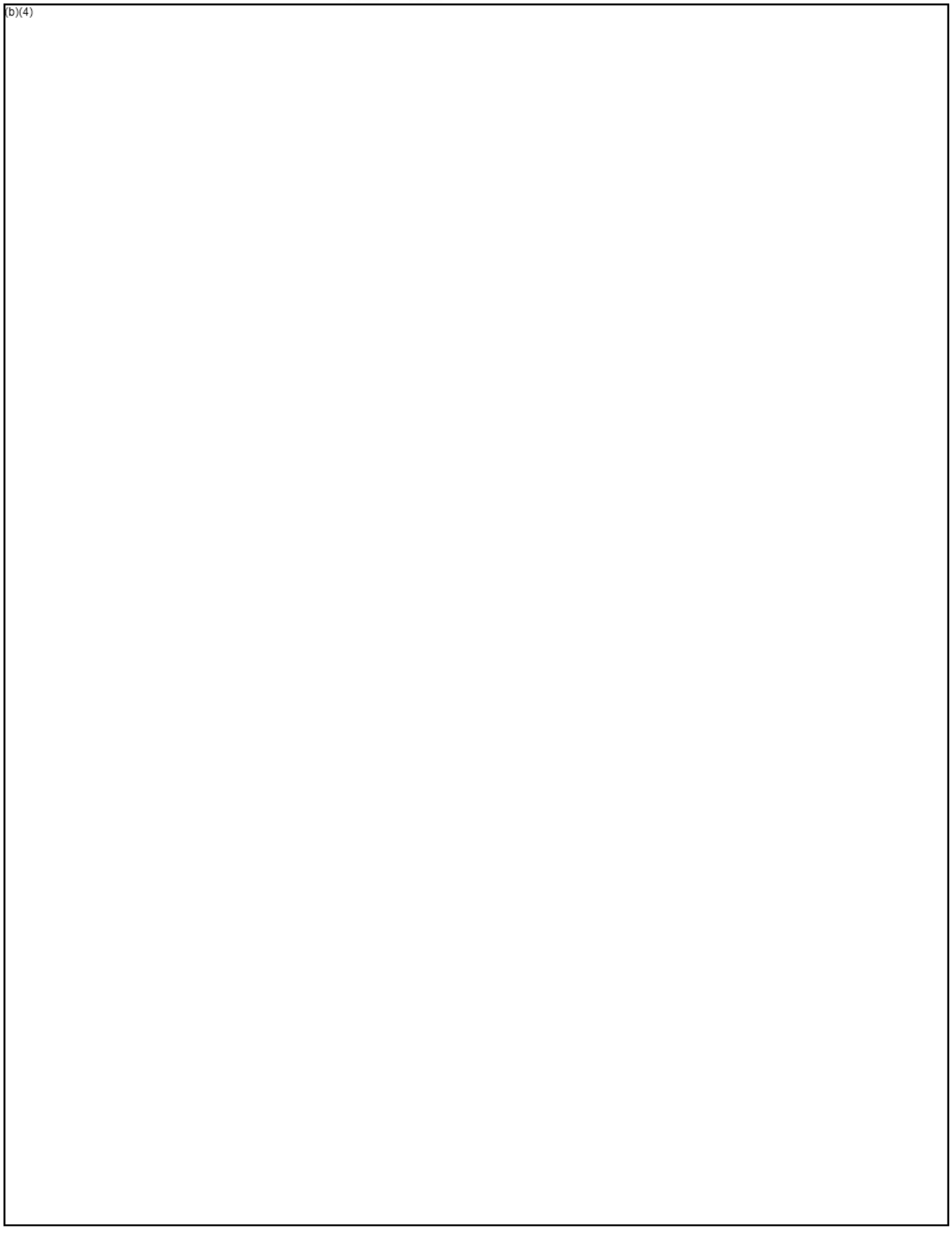
This agreement defines the conditions to be fulfilled by both parties.

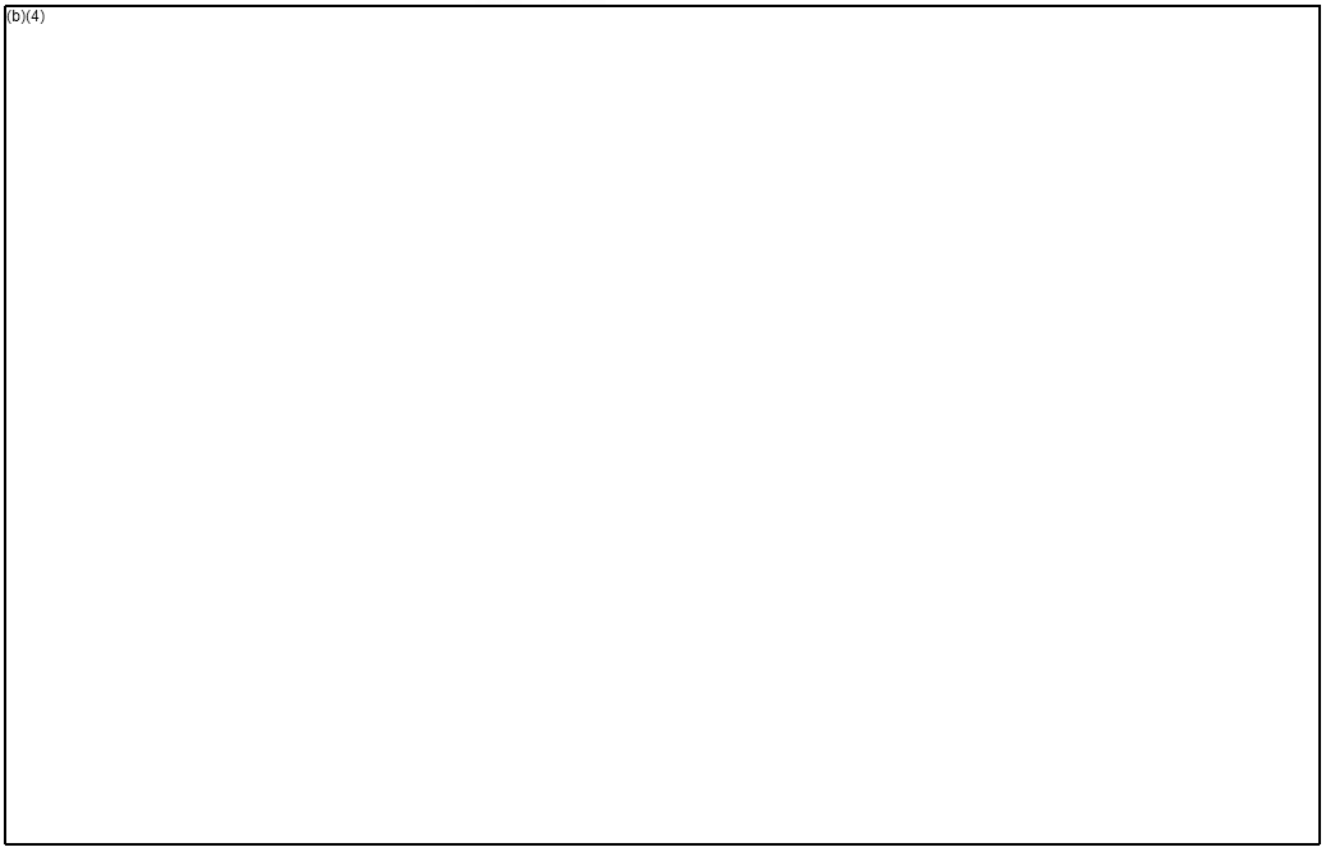
1. Scope of Agreement

The purpose of this Quality Agreement is to document the key responsibilities for the activities between Technical Resources International, Inc. (hereinafter referred to as "THE INSTITUTION") providing contracted support to (b)(6) hereinafter referred to as the "Sponsor")," and Janssen Research & Development, Division of Janssen R&D and affiliates (hereinafter referred to collectively as "THE COMPANY").

(b)(4)

(b)(4)




(b)(4)

(b)(4)


(b)(4)

(b)(4)

Signatures to Quality Agreement

Institution	Company
(b)(6) (b)(6) Technical Resources International, Inc. Office tel: (b)(6)	(b)(6) (b)(6) Qualified Person khimpens@its.jnj.com Office tel: +32/14/60.67.63
Signature: (b)(6) Digitally signed by (b)(6) Date: Date: 2020.09.17 11:55:14 -04'00'	Signature: (b)(6) Digitally signed by (b)(6) DN: c=US, o=JNJ, ou=Subscribers, cn=(b)(6) 0.9.2342.19200300.100.1.1=10015198 Reason: I am approving this document. Date: 2020.09.21 08:42:16 +02'00' Adobe Reader version: 11.0.10 Date:

QUALITY & SUPPLY CONTACTS FOR THE STUDY

Company

Function	Name	Contact Information
(b)(6)	(b)(6)	(b)(6) @its.jnj.com Office tel (b)(6)
(b)(6)	(b)(6)	(b)(6) @its.jnj.com Office tel: (b)(6)
(b)(6)	(b)(6)	(b)(6) @its.jnj.com Office tel: (b)(6)
Product Complaint Communications	NA	(b)(4)

Institution

Function	Name	Contact Information

CONFIDENTIAL DISCLOSURE AGREEMENT

WHEREAS the National Center of Advancing Translational Sciences ("NCATS"), a center of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), and Janssen Research and Development, LLC (the "Company"), having its place of business at 920 Route 202, PO Box 300, Raritan NJ 08869 (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial designated as Protocol ACTIV-1 IM titled "Randomized Master Protocol for Immune Modulators for Treating COVID-19 (the "Clinical Trial");"

WHEREAS the Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV").

WHEREAS the Biomedical Advanced Research and Development Authority (BARDA) is funding the Clinical Trial and NCATS is the designated NIH Center that will oversee the design and implementation of the Clinical Trial.

WHEREAS NCATS will conduct the Clinical Trial with a consortium of sites selected with assistance from HHS's contractor, Technical Resources International (TRI) Inc., and their subcontractors, Duke Clinical Research Institute (DCRI) and Syneos Health. Sites within the United States will be selected from the Clinical and Translational Science Awards (CTSA) Program and other selected sites under the leadership and coordination of DCRI, and international sites will be selected under the leadership and coordination of Syneos.

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, National Center for Advancing Translational Sciences ("NCATS"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS") and the Company (each a "Party" and collectively, the "Parties"), intending to be legally bound as of the date of the last signature hereto ("Effective Date"), agree that:

1. A Party ("Disclosing Party") may disclose information to the other ("Receiving Party") for the purpose of discussing a proposed collaboration on the Clinical Trial using Remicade (infliximab) for treatment of SARS CoV-2 ("Purpose") including the submission of an Investigational New Drug application to the FDA. The Disclosing Parties are: NCATS and the Company.

2. The information disclosed under this Agreement ("Confidential Information") is described as: any and all information associated with the Clinical Trial in so far as it relates to REMICADE (infliximab).

3. When the Receiving Party is NCATS, NCATS agrees not to share or disclose the Confidential Information of the Disclosing Party to any person except its employees, consultants or contractors of NCATS, investigators from the NCATS Trial Innovation

Network (TIN), employees, consultants or contractors of Biomedical Advances Research and Development Authority (BARDA), employees, consultants or contractors of the Foundation for the National Institutes of Health (FNIH) involved in the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership program, and members, consultants or contractors of Operation Warp Speed (OWS) to whom it is necessary to disclose the Confidential Information for the Purpose described above, always provided that any such disclosures shall be made under confidentiality terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information.

4. The Receiving Party's duties under this Agreement shall apply to any Confidential Information shared orally or in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked "Confidential." Oral disclosures must be reduced to writing, marked "Confidential" and sent to the Receiving Party's representative designated in Paragraph 9 within thirty (30) days after disclosure to be considered Confidential Information.

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or its Affiliates or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure in the possession of the Receiving Party or its Affiliates; (c) is acquired by the Receiving Party or its Affiliates from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party or its Affiliates, without reference to the information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes the Receiving Party to disclose.

   In addition, Parties acknowledge that the Company or the Company's Affiliates, may currently or in the future have internal research or development programs relating to or competing with one or more aspects of the Confidential Information and without recourse to the Confidential Information disclosed hereunder and may undertake development programs at a future date or may receive information on the same or related subject matter from a third party and may develop and commercialize products relating to such subject matter independently or in cooperation with such third party.

6. At the request of the Disclosing Party, the Receiving Party agrees to return or destroy, at the discretion of the Receiving Party, all Confidential Information received, except that the

Receiving Party may retain in its confidential files one (1) copy of written Confidential Information for record purposes only.

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required to disclose any of the Confidential Information, the Receiving Party first uses reasonable efforts to preserve the confidentiality of the Information and shall provide the Disclosing Party with timely notice and, to the extent practicable, consult with the Disclosing Party prior to any disclosure.

8. Each Disclosing Party expressly represents that it is the owner of or has control over and that it has full right and authority to disclose the Confidential Information to the Disclosing Party and that the Receiving Party shall not incur any liability merely for using the Confidential Information disclosed by the Disclosing Party for the Purpose.

9. Except as otherwise expressly provided for herein, this Agreement does not convey any rights under the know-how, patents or other intellectual property rights of either party nor does it create any such obligations.

10. This Agreement is made under and shall be construed in accordance with Federal laws as applied by the Federal Courts in the District of Columbia, and constitutes the entire understanding between the Parties with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for five (5) years from the Effective Date.

11. Notices or other communications required to be sent to NCATS under this Agreement shall be sent in writing and addressed to (b)(6) Office of Strategic Alliances, National Center for Advancing Translational Sciences, 9800 Medical Center Drive, Room 3202B, Rockville, MD 20850, email: (b)(6) @nih.gov. Notices required to be sent to Company under this Agreement shall be in writing and addressed to 920 Route 202, PO Box 300, Raritan NJ 08869, Attention Legal Department.

12. *Counterparts; Facsimile and Electronic Transmission.* This Agreement may be executed in counterparts (and by different parties hereto on different counterparts), each of which shall constitute an original but all of which when taken together shall constitute a single contract, and shall become effective as of the date first written above. Delivery of an executed signature page to this Agreement by facsimile or electronic transmission (such as by an email with pdf attachment) shall be as effective as delivery of a manually signed counterpart of this Agreement.

REMAINDER OF PAGE INTENTIONALLY LEFT BLANK

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Center for Advancing Translational Sciences (NCATS),
National Institutes of Health (NIH)
6701 Democracy Blvd, Suite 900
Bethesda, MD 20817

Authorized Signature:

(b)(6) Weingarten -S Digitally signed by (b)(6) (b)(6) Date: 2020.08.31 12:30:44 -04'00'

(b)(6)
Director, Office of Strategic Alliances

Date:_____

Janssen Research & Development, LLC
920 Route 202, PO Box 300, Raritan NJ 08869

Authorized Signature: (b)(6)

Name: (b)(6)
Title: (b)(6)

Date : 31 Aug. 2020

CONFIDENTIAL DISCLOSURE AGREEMENT

WHEREAS the National Center of Advancing Translational Sciences ("NCATS"), a center of the National Institutes of Health ("NIH"), which is part of the United States ("U.S.") Government Department of Health and Human Services ("HHS"), and Gilead Sciences, Inc. (together with its affiliates and subsidiaries, the "Company"), located at 333 Lakeside Drive, Foster City, CA 94404 (each a "Party," and together, the "Parties") have agreed to cooperate in the conduct of a clinical trial designated as Protocol ACTIV-1 IM titled "Randomized Master Protocol for Immune Modulators for Treating COVID-19;"

WHEREAS this Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV").

WHEREAS the Biomedical Advanced Research and Development Authority (BARDA) is funding this trial and NCATS is the designated NIH Center that will oversee the design and implementation of the trial.

WHEREAS NCATS will conduct this Clinical Trial with a consortium of sites selected with assistance from HHS contractor, Technical Resources International (TRI) Inc., and their subcontractors Duke Clinical Research Institute (DCRI) and Syneos Health. Sites within the United States will be selected from the Clinical and Translational Science Awards (CTSA) Program and other selected sites under the leadership and coordination of DCRI, and international sites will be selected under the leadership and coordination of Syneos.

In order to protect confidential information relating to research, development, business plans and other technology, which may be disclosed between them, National Center for Advancing Translational Sciences ("NCATS"), a component of the National Institutes of Health ("NIH"), an agency of the U.S. Department of Health and Human Services ("HHS") and Gilead Sciences, Inc. (together with its affiliates and subsidiaries, the "Company") (each a "Party" and collectively, the "Parties"), intending to be legally bound as of the date of the last signature hereto ("Effective Date"), agree that:

1. A Party ("Disclosing Party") may disclose information to the other ("Receiving Party") for the purpose of discussing a proposed collaboration on ACTIV-1 IM, entitled, " Randomized Master Protocol for Immune Modulators for Treating Covid-19" using remdesivir for treatment of SARS CoV-2 ("Purpose"). The Disclosing Parties are: NCATS and Company.

2. The information disclosed under this Agreement ("Confidential Information") is described as: any and all non-public information and documents associated with clinical trials investigating SARS CoV-2 and Company's products.

3. When the Receiving Party is NCATS, NCATS agrees not to share or disclose the Confidential Information of the Disclosing Party to any person except its employees, consultants or contractors of NCATS, investigators from the NCATS Trial Innovation Network (TIN), employees, consultants or contractors of Biomedical Advances Research and Development Authority (BARDA), employees, consultants or contractors of the Foundation for the National Institutes of Health (FNIH) involved in the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership program, and members, consultants or contractors of Operation Warp Speed (OWS) to whom it is necessary to disclose the Confidential Information for the Purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. When the Receiving Party is Company, Company will not disclose the Confidential Information of the Disclosing Party to any person except its employees, consultants, or contractors to whom it is necessary to disclose the Confidential Information for the purpose described above, and any such disclosures shall be under terms at least as restrictive as those specified herein. Any of the persons who are given access to the Confidential Information shall be informed of this Agreement. The Receiving Party shall protect the Confidential Information by using the same degree of care, but no less than a reasonable degree of care, as the Receiving Party uses to protect its own confidential information.

4. The Receiving Party's duties under this Agreement shall apply to any Confidential Information shared orally or in any written document, memorandum, report, correspondence, drawing or other material, or computer software or program, developed or prepared by the Disclosing Party or any of its representatives that has been clearly marked "Confidential." Oral disclosures must be reduced to writing, marked "Confidential" and sent to the Receiving Party's representative designated in Paragraph 9 within thirty (30) days after disclosure to be considered Confidential Information. Notwithstanding the foregoing, if such information is not marked as "Confidential" but it is reasonably evident to be confidential by reason of its character or the circumstances or the manner of its disclosure, then such information shall be considered Confidential Information hereunder.

5. Notwithstanding any other provision of this Agreement, Confidential Information shall not include any item of information, data, patent or idea that: (a) is within the public domain prior to the time of the disclosure by the Disclosing Party to the Receiving Party, or thereafter becomes within the public domain, other than as a result of disclosure by the Receiving Party or any of its representatives in violation of this Agreement; (b) was, on or before the date of disclosure in the possession of the Receiving Party; (c) is acquired by the Receiving Party from a third party not under an obligation of confidentiality; (d) is hereafter independently developed by the Receiving Party, without reference to the information received from the Disclosing Party; or (e) the Disclosing Party expressly authorizes the Receiving Party to disclose.

6. At the request of the Disclosing Party, the Receiving Party agrees to return all Confidential Information received, except that the Receiving Party may retain in its confidential files one (1) copy of written Confidential Information for record purposes only.

7. If the Receiving Party, or anyone to whom it discloses the Confidential Information in accordance with Paragraph 3, becomes legally required to disclose any of the Confidential Information, the Receiving Party shall provide the Disclosing Party with timely notice and, to the extent practicable, consult with the Disclosing Party prior to any disclosure.

8. This Agreement is made under and shall be construed in accordance with Federal laws as applied by the Federal Courts in the District of Columbia, and constitutes the entire understanding between the Parties with respect to the subject matter hereof and merges any and all prior agreements, understandings and representations. This Agreement may not be superseded, amended or modified except by written agreement between the Parties. This Agreement will control Confidential Information disclosed only between the Effective Date and one (1) year thereafter and will otherwise remain in effect for three (3) years from the Effective Date.

9. Notices or other communications required to be sent to NCATS under this Agreement shall be sent in writing and addressed to (b)(6) Office of Strategic Alliances, National Center for Advancing Translational Sciences, 9800 Medical Center Drive, Room 3202B, Rockville, MD 20850, email: (b)(6) @nih.gov. Notices required to be sent to Company under this Agreement shall be in writing and addressed to Gilead Sciences, Inc., Corporate Legal, 333 Lakeside Drive, Foster City, CA 94404, email: (b)(4) fax: (b)(4) .

10. Each Party has caused this Agreement to be executed on its behalf in duplicate (each of which duplicate shall be deemed to be an original).

REMAINDER OF PAGE INTENTIONALLY LEFT BLANK

Accepted and agreed by the Parties through their duly authorized representatives as of the last date of signature below.

National Center for Advancing Translational Sciences (NCATS),
National Institutes of Health (NIH)
6701 Democracy Blvd, Suite 900
Bethesda, MD 20817

Authorized Signature:

(b)(6)

Digitally signed by (b)(6)
(b)(6)
Date: 2020.09.09 18:26:38 -04'00'

(b)(6)
Director, Office of Strategic Alliances

Date:_____

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Authorized Signature:

(b)(6)

(b)(6)

(b)(6)

Date : Sept 9, 2020

CLINICAL TRIAL MATERIAL SUPPLY AGREEMENT

THIS AGREEMENT (the "**Agreement**") is made as of October 8, 2020 (the "**Effective Date**").

1. PARTIES

1.1 **GILEAD SCIENCES, INC.**, a Delaware corporation with executive offices at 333 Lakeside Drive, Foster City, California 94404 ("GILEAD"); and

1.2 **THE NATIONAL CENTER ON ADVANCING TRANSLATIONAL SCIENCES**, a component of the National Institutes of Health (NIH) with executive offices at 6701 Democracy Blvd. Suite 900, Bethesda, MD 20817 ("RECIPIENT"); and

Each of GILEAD and RECIPIENT shall be referred to herein as a "Party" and, collectively, they shall be referred to as the "Parties".

2. BACKGROUND

2.1 GILEAD holds rights in the GILEAD STUDY DRUG (as hereinafter defined).

2.2 RECIPIENT desires to conduct the Clinical Trial ACTIV1 IM entitled "Randomized Master Protocol for Immune Modulators for Treating COVID-19" (as hereinafter defined) utilizing the GILEAD STUDY DRUG and OTHER STUDY DRUG (as hereinafter defined).

2.3 GILEAD has agreed to supply RECIPIENT with certain quantities of GILEAD STUDY DRUG in accordance with this Agreement to enable RECIPIENT to carry out the Clinical Trial (as hereinafter defined).

2.4 Nothing contained in this Agreement shall be construed, by implication or otherwise, as a further commitment or obligation by either Party to enter into any further agreement or as the grant of a license to RECIPIENT to use GILEAD STUDY DRUG other than as expressly set forth in this Agreement. Nothing contained in this Agreement shall be construed, by implication or otherwise, as the grant of a license to GILEAD to use the OTHER STUDY DRUG.

3. DEFINITIONS

The following definitions shall apply in this Agreement:

3.1 **"Award"** - any one or more, as appropriate, of the Government contracts, grants, or cooperative agreements between a Government agency and the awardee, who may subcontract with the Clinical Research Sites.

3.2 **"Background Invention"** – any inventions conceived and first actually or constructively reduced to practice (as documented by competent written records) before the Effective Date of this Agreement, or otherwise outside the scope of this Agreement.

3.3 **"Clinical Trial"** – the clinical study to be conducted pursuant to the Protocol by Investigators at Study Centers.

3.4 **"Confidential Information"** – all information provided by the Disclosing Party (as hereinafter defined) to the Recipient Party, whether written, electronic, visual, or oral, and in any form including, without limitation, information relating to the Disclosing Party's proprietary drug, pricing data, financial data, information technology-related research and development plans, manuals, reports, patent applications, trade secrets and Inventions, including Background Inventions.

3.5 "**CRFs**" – the completed case report forms for the Clinical Trial.

3.6 **"Data"** – all results and data generated during the conduct of the Clinical Trial and all completed CRFs relating to the GILEAD STUDY DRUG or combination of GILEAD STUDY DRUG and OTHER STUDY DRUG, but shall not include Inventions, raw data, or patient records.

3.7 **"Disclosing Party"** – the Party which discloses its Confidential Information to the Recipient Party.

3.8 **"GILEAD STUDY DRUG"** – remdesivir supplied by GILEAD under the terms of this Agreement specifically for the Clinical Trial.

3.9 "**Health Authority**" – the United States Food and Drug Administration (or its successor agency) or comparable agencies in foreign countries performing similar functions.

3.10 **"Inventions"** – any invention or discovery that is or may be patentable or otherwise protected under 35 U.S.C., or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act, 7 U.S.C. §§ 2321 et seq.

3.11 "**Investigators**" – the principal investigators carrying out the Clinical Trial as designated from time to time by RECIPIENT.

3.12 "**Investigators Brochure**" or "**IB**" - in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the GILEAD STUDY DRUG, including animal screening, preclinical toxicology and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the GILEAD STUDY DRUG or related drugs, and

precautions, such as additional monitoring, to be taken as part of the investigational use of the GILEAD STUDY DRUG.

3.13 "**OTHER STUDY DRUGS**" – Abatacept/Orencia, Infliximab/Remicade and/or Cenicriviroc/CVC

3.14 "**Protocol**" –. means the formal, detailed description of the Clinical Trial to be performed as provided in Protocol ACTIV-1 IM, "Randomized Master Protocol for Immune Modulators for Treating COVID-19" and any company/product specific associated appendices. The Protocol describes the objective(s), design, methodology, statistical considerations and organization of a clinical trial. The Agreement will be governed by the most recent version of the Protocol, and should the Agreement be executed prior to complete finalization of the Protocol, the last-dated version thereof will be considered to be incorporated by reference in place of any prior versions. In the event that there is a conflict between the terms of the Protocol and the terms of the Agreement, the terms of the Agreement will govern.

3.15 "**Protocol Teams**" – the teams, under the direction of RECIPIENT, responsible for the development and management of the Protocol, evaluation of data, proposal of amendments, and all issues related to the Protocol or aspects of Protocol development and modification. (b)(4)

(b)(4)

3.16 **"Recipient Party"** – the Party which receives Confidential Information from the Disclosing Party.

3.17 "**Study Centers**" – the study centers for the Clinical Trial as designated by RECIPIENT from time to time.

3.18 "**Technical Resources International, Inc." or "TRI**" means HHS contractor and their subcontractors, "Duke Clinical Research Institute" or "DCRI" and "Syneos Health" or "Syneos" and "Fisher BioServices" or "Fisher," and is the organization that schedules, tracks, reports, stores, modifies, transmits and processes regulatory, safety, data management and other activities for this Clinical Trial. TRI operates pursuant to a statement of work contained within an Award between BARDA and TRI. BARDA has named NCATS as its designee in the management of the statement of work in the awarded contract with TRI.

4. COMMENCEMENT

This Agreement shall be effective as of the Effective Date.

5. INVESTIGATORS AND RESEARCH STAFF

5.1 Clinical Trial. RECIPIENT has designed the Clinical Trial. GILEAD wishes to provide the GILEAD STUDY DRUG for the Clinical Trial as per Article 6.2.

5.2 RECIPIENT will be responsible for contracting with TRI who will sub-contract with Investigators and Study Centers for the conduct of the Clinical Trial.

5.3 Investigators. The Clinical Trial will be conducted by the Investigators sub- contracted through TRI.

5.4 Contracting by RECIPIENT. This Clinical Trial is part of a COVID-19 treatment and prevention research endeavor and public-private partnership supported by Accelerating COVID-19 Therapeutic Interventions and Vaccines ("ACTIV"). Under Operation Warp Speed, the Biomedical Advanced Research and Development Authority (BARDA) is funding this trial via a contract with Technical Resources International, Inc. (TRI) and has named NCATS as the TRI contract designee in which NCATS will oversee the design and implementation of the Clinical Trial. NCATS will conduct this Clinical Trial with a consortium of sites selected with assistance from TRI, and their subcontractors Duke Clinical Research Institute (DCRI) and Syneos Health ("Syneos"). Sites within the United States will be selected from the Clinical and Translational Science Awards (CTSA) Program and other selected sites under the leadership and coordination of DCRI, and international sites will be selected under the leadership and coordination of Syneos. In the event that any other Clinical Research Sites are included in this Clinical Trial in order to complete enrollment, these sites will meet NCATS standards for clinical research sites conducting research sponsored by NCATS. BARDA, TRI, DCRI, Syneos and the Clinical Research Sites and their respective Investigators are not parties to this Agreement.

5.5 Obligations. RECIPIENT confirms that the obligations of TRI described in this Agreement are consistent with the terms of the Awards in place for the conduct of the Clinical Trial.

5.6 Delegation of Duties by Investigators. U.S. Department of Health and Human Services contractor, TRI, may delegate duties and responsibilities to sub-investigators or research staff only to the extent permitted by the applicable Health Authority and regulations governing the conduct of

clinical investigations. TRI and its subcontractor Investigators shall still be obligated for those duties and responsibilities delegated to third parties.

5.7 Compliance with Institutional Policies. RECIPIENT will require in each Award that Investigators comply with the policies and procedures of the organization(s) with which that Investigator is affiliated, including applicable financial policies. RECIPIENT will notify GILEAD within a reasonable time and in any event within five (5) days of any conflict of which it becomes aware between the applicable terms of this Agreement and any such policy or procedure in regard to any Investigator, and the Parties will attempt to reach an appropriate accommodation.

6. PROTOCOL REVIEW AND COMMENT/STUDY DRUG/SAFETY REPORTING

6.1 (b)(4)

6.2 GILEAD (b)(4) per agreed upon schedule with (b)(4)
(b)(4)

6.3 RECIPIENT through TRI shall report safety information to GILEAD as follows:

(a) GILEAD STUDY DRUG safety definitions used in this Agreement shall be interpreted in accordance with the Protocol and made a part hereof.

(b) RECIPIENT will collect safety reports according to the procedure outlined in the Protocol. RECIPIENT through TRI will be responsible for the management of safety data from the Clinical Trial and any associated regulatory reporting obligations for individual or periodic safety reports to appropriate authorities (including the FDA), Investigators, and applicable IRBs, in compliance with all applicable laws, rules and regulations, and the requirements of the IRBs.

(c) For any safety events collected according to the Protocol that meet all of the following criteria of (i) Serious (ii) Unexpected and (iii) Suspected Adverse

Reaction, RECIPIENT through TRI will provide to GILEAD a completed copy of the IND safety report at the time the report is submitted to the FDA, RECIPIENT through TRI will provide follow up information to GILEAD at the time the follow up safety report is submitted to FDA. The reporting will be completed in the timeframes consistent with 21 CFR 312.32.

(d) RECIPIENT through TRI will report all other safety events collected according to the Protocol not covered by 3.3.3 to the FDA and to GILEAD on a timely basis consistent with 21 CFR Part 312.33.

(e) RECIPIENT through TRI will alert GILEAD's Pharmacovigilance and Epidemiology (PVE) at the address below of any potential safety issues or any Protocol amendments or changes to the Informed Consent Form for the Clinical Trial arising from a safety concern associated with the GILEAD STUDY DRUG within fifteen (15) calendar days of Clinical Trial Sponsor first becoming aware of such event.

(f) RECIPIENT through TRI will report in English all safety information as defined below, which includes, but is not limited to:

i. all Serious Adverse Events (SAEs) related to the GILEAD STUDY DRUG no later than 15 calendar days of Clinical Trial Sponsor first becoming aware of such events, provided on the unprocessed SAE form, which has not yet been medically reviewed; and

ii. all SAEs (b)(4) (b)(4) and

iii. (b)(4)

(g) All safety reports addressed to GILEAD must be sent to the attention of the GILEAD safety contact at:

Gilead Sciences, Inc.
Pharmacovigilance & Epidemiology
333 Lakeside Dr.
Foster City, CA 94404
Fax: (b)(4)
Tel: (b)(4)
E-mail: Safety_FC@gilead.com

(h) Upon GILEAD's request, and subject to any restrictions in applicable policies for the Clinical Trial, RECIPIENT through TRI will provide any additional information required to perform medical assessments of any safety information provided to GILEAD, including the provision of data in

relation to blinded data if applicable. Upon GILEAD's request, and subject to any restrictions in applicable policies for the Clinical Trial and upon RECIPIENT's determination that the report can be unblinded without undermining the scientific integrity of the Clinical Trial, RECIPIENT through TRI will provide unblinding information for reports that are assessed as Serious and Unexpected Suspected Adverse Reactions (SUSARs). Unblinding information for OTHER STUDY DRUG as a suspect product will be redacted and provided to Gilead either at the time of provision of the completed copy of the IND safety report to Gilead as per 6.3(c) above or upon request but within the timelines as defined in section 6.3(f)(i) above. RECIPIENT will provide GILEAD all reasonable assistance in providing any further information requested by GILEAD. GILEAD will send any such request for additional information to RECIPIENT's contractor, TRI's safety contact identified below:

TRISafetyOffice@tech-res.com

(i) (b)(4)

(j) (b)(4)

(k) RECIPIENT through TRI will provide GILEAD with a copy of the IND Annual Report), as well as any formal correspondence with the FDA related to the GILEAD STUDY DRUG and the Clinical Trial. RECIPIENT through TRI will verify that Clinical Trial-related submissions to the Health Authorities were made in accordance with applicable laws, rules, regulations and guidelines.

(l) require in each Award that Investigators report safety information in accordance with this Article 6.3.

6.4 GILEAD represents and warrants that upon delivery to RECIPIENT the GILEAD STUDY DRUG will be in compliance with specifications and applicable laws and regulations relating to drugs intended for investigational use in humans.

6.5 RECIPIENT shall require that the Investigators and Clinical Trial subjects use the GILEAD STUDY DRUG solely in connection with the Clinical Trial. (b)(4)

(b)(4)

6.6 GILEAD will provide a current IB in eCTD format for all applicable components of the GILEAD STUDY DRUG, and any later revisions and addenda to the IB for the GILEAD STUDY DRUG, including a summary of changes (SOC), to NCATS as mutually agreed by the Parties, who will agree to keep them in confidence in accordance with Article 12 (Confidentiality) of this Agreement. GILEAD agrees to provide NCATS as mutually agreed by the Parties, any updated version of the IB, with the SOC, within fifteen (15) days of issuance. GILEAD will send the IB and SOC to the NCATS to the attention of the NCATS contact for regulatory matters identified in Article 15, or to NCATS' designee. NCATS through TRI or its subcontractors, will distribute the IB to the Study Centers. NCATS will address requests for IBs, including updated versions and SOCs, to:

Gilead Sciences, Inc.
Attn: (b)(6)
(b)(6)
333 Lakeside Drive
Foster City, CA 94404
Phone:
E-mail: (b)(6) @gilead.com

7. STUDY CONDUCT

7.1 Sponsorship. Dr. Daniel Benjamin ("Clinical Trial Sponsor"), an employee of DCRI, the subcontractor of RECIPIENT's contractor TRI, not GILEAD, is the IND sponsor of the Clinical Trial. RECIPIENT through TRI will notify Investigators that they should not represent to any third party, including Clinical Trial subjects, that GILEAD is a sponsor of the Clinical Trial.

7.2 Regulatory. RECIPIENT through TRI is solely responsible for any and all regulatory obligations associated with the conduct of the Clinical Trial, including, but not limited to, obtaining and maintaining an Investigational New Drug application (IND) and submission and approval of relevant clinical trial applications if required for OTHER STUDY DRUG. RECIPIENT through TRI has delegated regulatory obligations to one or more third parties to facilitate RECIPIENT's oversight, monitoring, and administration of the Clinical Trial at Study Centers outside of the United States. RECIPIENT through TRI will submit any clinical trial application and subsequent reports to all applicable regulatory authorities outside of the United States. (b)(6)

(b)(4)

7.3 Standards. RECIPIENT will, and will require in the Awards that Investigators, conduct the Clinical Trial in accordance with the Protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, and all applicable governmental laws, rules, and regulations.

7.4 IRB Approval. RECIPIENT will ensure, and require in the Awards, that the Clinical Trial is approved by and subject to continuing oversight by an appropriate Institutional Review Board (IRB) in the United States.

7.5 Informed Consent. RECIPIENT will ensure, and require in the Awards that, Investigators obtain informed consent for each Clinical Trial subject in accordance with 21 Code of Federal Regulations Part 50 in the United States and in accordance with ICH-GCPs or applicable regulations in other countries regarding informed consent. GILEAD shall be allowed to review and comment on the sample informed consent form solely as it relates to the use of the GILEAD STUDY DRUG and RECIPIENT shall include language provided by GILEAD related thereto.

7.6 HIPAA Authorization or Waiver. RECIPIENT will ensure, and require in the Award that, Investigators will obtain authorization or waiver of

authorization, as applicable, for the use or disclosure of health information from each Clinical Trial subject in accordance with relevant laws and regulations and as contemplated under this Agreement.

7.7 Duration of Clinical Trial. RECIPIENT shall use reasonable efforts to complete the Clinical Trial in accordance with the Protocol. Notwithstanding the foregoing or any other provision to the contrary in this Agreement, RECIPIENT reserves the right to cancel or terminate the Clinical Trial at any time, in its sole discretion.

7.8 Compliance. The Parties shall comply with all applicable laws and regulations.

8. TERM AND TERMINATION

8.1 This Agreement shall expire upon the termination or expiration of the Clinical Trial, unless terminated earlier pursuant to the terms of this Agreement. RECIPIENT may cancel or terminate the Clinical Trial at any time, in its sole discretion.

8.2 This Agreement shall be immediately terminable by either Party in the event that the other Party commits a material breach of this Agreement that shall not have been remedied within thirty (30) days after receipt of written notice of such breach by such breaching Party from the nonbreaching Party, unless such material breach is not capable of remedy in which case the notice period shall not apply. In the event the breaching Party has not fully remedied such material breach within the thirty (30) day period following receipt of written notice as described in the foregoing sentence, but can show reasonable and continuing diligence to remedy such material breach, then the thirty (30) day time limit in the foregoing sentence shall be extended for a reasonable period of time, not to exceed ninety (90) days.

8.3 Either Party may terminate this Agreement at any time and for any reason with sixty (60) days prior written notice to the other Party. However, during such notice period, the Parties shall, as applicable, make good faith efforts to resolve any and all issues related to the Party's election to so terminate. RECIPIENT will be responsible for, at GILEAD's discretion, the return to GILEAD (at GILEAD's expense) or destruction of any unused GILEAD STUDY DRUG at the Study Centers, upon completion or earlier termination of the Clinical Trial.

8.4 The Parties agree that should this Agreement be terminated prior to completion of the Clinical Trial; the Clinical Trial will be completed if medically appropriate. In that event, each enrolled human subject will be followed through the period outlined in the Protocol and (b)(6)

(b)(4)

8.5 Upon termination or expiration, RECIPIENT shall have no further obligations to GILEAD, except as set forth in those provisions that specifically survive the termination or expiration of this Agreement.

9. INTELLECTUAL PROPERTY

9.1 Ownership of any Invention conceived solely or jointly by RECIPIENT employees, the Study Centers and Investigators, or other RECIPIENT contractors or grantees as a consequence of conducting the Clinical Trial, will be determined under U.S. laws pertaining to intellectual property created in the course of federally funded research. Neither Party acquires by virtue of this Agreement any right, title, nor interest in or to any issued Patents or pending patent applications owned or controlled by the other Party as of the date of this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by the GILEAD to the RECIPIENT.

9.2 NCATS Intellectual Property.

(a) The Government will retain title to any Patent, pending patent applications or other intellectual property rights in Inventions conceived solely by RECIPIENT employees in the course of the Clinical Trial.

(b) The RECIPIENT agrees to notify GILEAD of any RECIPIENT sole or joint Invention and to disclose it to GILEAD under an appropriate confidentiality agreement. GILEAD may apply for nonexclusive or exclusive license rights to any such patentable Invention made by RECIPIENT employees that might arise during the Clinical Trial and the RECIPIENT will consider the GILEAD's application for a nonexclusive or exclusive license consistent with 37 C.F.R. Part 404.

9.3 GILEAD Intellectual Property. GILEAD will retain title to any patents, pending patent applications, or other intellectual property rights in Inventions conceived by its employees during the course of the Clinical Trial.

9.4 Study Center/Investigator Intellectual Property.

(a) This Agreement does not grant any license or obligation to license any intellectual property of the Study Centers or preclude the creation of intellectual property rights, including but not limited to Inventions conceived by the Investigators or other RECIPIENT contractors or grantees during the course of the clinical research. GILEAD may enter into a separate agreement with the Clinical Research Site or Investigators, regarding intellectual property rights and confidentiality that do not interfere with the conduct of this Clinical Trial, contradict the terms of this Agreement or contradict the terms of the Award with RECIPIENT.

9.5 Joint RECIPIENT-GILEAD Intellectual Property. The RECIPIENT and GILEAD will have joint intellectual property rights in Inventions conceived jointly by their employees during the course of the clinical research. GILEAD may apply for a non-exclusive or exclusive license to the RECIPIENT rights in such Inventions in accordance with the 37 CFR 404.

9.6 NCATS represents and certifies that any intellectual property rights granted to any third party collaborator providing OTHER STUDY DRUG for the Clinical Trial will not be greater than any intellectual property rights provided to Gilead under this Agreement, and in all cases consistent and compliant with 37 CFR 404 and other applicable regulations and policies.

10. CLINICAL STUDY STATUS AND RESULTS

10.1 GILEAD will be informed about the progress of the Clinical Trial (b)(4) (b)(4) RECIPIENT through its contractor shall also provide GILEAD with the final Clinical Study Report (CSR) immediately following submission to any Health Authorities. All reports provided under this section 10.1 are deemed to be RECIPIENT Confidential Information.

10.2 All medical records of Clinical Trial subjects under this Agreement shall remain the property of RECIPIENT through TRI or the Study Center, as applicable. RECIPIENT through TRI will require that Investigators record all Clinical Trial related Data from the original patient records onto the CRFs for the Clinical Trial. RECIPIENT through TRI shall retain a copy of all raw data recorded in the conduct of the Clinical Trial and all completed CRFs for the Clinical Trial and all other Clinical Trial documents in compliance with RECIPIENT's policies and all applicable laws. All data obtained from the Clinical Trial will be in the custody of TRI and its sub-awardees Investigator or the Study Center, as applicable, which produces such data. Without limiting Section 15, (b)(4)

(b)(4)

11. BIOLOGICAL SAMPLES

11.1 Collection, Retention and Use of Biological Samples. Specimens collected during the Clinical Trial as set forth in the Protocol ("**Biological Samples**") may include, without limitation, blood, serum, collected from subjects enrolled in the Clinical Trial. Biological Samples further include, without limitation, any tangible material directly or indirectly derived from such blood, fluid or tissue samples, such as: genes, gene fragments, gene sequences, proteins, protein fragments, protein sequences, probes, DNA, RNA, cDNA libraries, plasmids, vectors, expression systems, cells, cell lines, organisms, antibodies or other biological substances; and any constituents, progeny, mutants, variants, derivatives, replications, reagents or chemical compounds thereof or derived therefrom. RECIPIENT through its contractor shall only use the Biological Samples from Clinical Trial subjects in accordance with the Protocol and informed consent form.

11.2 RECIPIENT's Use of Biological Samples. RECIPIENT, through its contractor may receive quantities of Biological Samples from Study Centers, as set forth in the Protocol or informed consent form, for use in the research specified in the Protocol or informed consent form provided that such research complies with all applicable laws and regulations, including, but not limited to, patient privacy and informed consent laws.

(b)(4)

12. CONFIDENTIALITY

12.1 Each of the Parties agrees that all Confidential Information of the Disclosing Party shall remain the sole and exclusive property of the Disclosing Party during the term of this Agreement and thereafter.

12.2 (b)(4)

(b)(4) Further, each Party agrees to take all reasonable precautions to prevent the disclosure by any of its employees, officers or agents of the Disclosing Party's Confidential Information to any third party or otherwise into the public domain. Each Party agrees as a Recipient Party that neither it, nor any employee or agent will be permitted to make any use of the Disclosing Party's Confidential Information except as permitted by this Agreement.

12.3 A Recipient Party may disclose the Disclosing Party's Confidential Information to the extent such disclosure is required to comply with applicable governmental regulations or to the extent ordered by a court exercising its right of authority over such Recipient Party provided that if a Recipient Party is required by such applicable law or court to make any such disclosure of Confidential Information, such Recipient Party will give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable best efforts to secure confidential treatment of the Confidential Information required to be disclosed.

(b)(4)

12.4 The provisions of this Section 12 do not apply to any Confidential Information which the Recipient Party demonstrates:

(a) was known to Recipient Party prior to receiving that information either directly or indirectly from Disclosing Party, as demonstrated by competent written records;

(b) is generally known to the public or which becomes generally known to the public through no act or omission on the part of Recipient Party; or

(c) is rightfully disclosed to Recipient Party at any time by a third party not a party to this Agreement without restriction.

12.5 Any and all of the Disclosing Party's Confidential Information received by Recipient Party, or any of its employees, officers or agents, in whatever form, including all copies or duplicates made or retained by Recipient Party, or any of its employees, officers or agents, shall be promptly returned to Disclosing Party upon written request by Disclosing Party, as the case may be, or disposed of in accordance with the written instructions of the Disclosing Party. The Recipient Party may retain one copy in its legal archives solely for purposes of monitoring its surviving obligations under this Agreement.

12.6 The obligations of this Section 12 shall terminate seven (7) years following termination or expiration of this Agreement.

13. REPRESENTATIONS, WARRANTIES AND CERTAIN COVENANTS

13.1 Each Party represents and warrants to the other Party that:

(a) it has legal power, authority and right to enter into this Agreement and to perform its respective obligations in this Agreement; and

(b) it is not, as of the Effective Date, a party to any agreement, arrangement or understanding with any third party that prevents it from fulfilling any of its obligations under the terms of this Agreement;

13.2 Additionally, GILEAD represents and warrants to RECIPIENT that:

(a) (b)(4)

13.3 Additionally, RECIPIENT represents and warrants to GILEAD that:

(a) to its knowledge, the Study Center's personnel, facilities and patient population are adequate to perform the Study Center's obligations under the Protocol;

(b) it shall comply, and shall include provisions in each Award that the Study Center and Investigator shall comply with Health Authority reporting requirements, including those related to adverse event reporting, and all reporting requirements set forth in the Protocol and the PVA or as required by applicable laws;

(c) RECIPIENT will not permit any person or entity directly involved in the conduct of the Clinical Trial to use in any capacity the services of any person who has been debarred or disqualified by the Health Authority pursuant to the Generic Drug Enforcement Act of 1992 or any other equivalent or successor statutes, rules or regulations. RECIPIENT agrees and undertakes to promptly notify GILEAD in writing if it becomes aware that any such person or entity has been debarred or disqualified or proceedings have been initiated with respect to debarment or disqualification, whether such debarment or initiation of proceedings occurs during or after the performance of the Clinical Trial.

14. PUBLICITY AND PUBLICATION

14.1 Neither Party shall publicly disclose the terms of this Agreement without the prior written consent of the other Party, provided that RECIPIENT may disclose the terms on a need to know basis to the Study Centers or the Investigators and/or other grantees, contractors or consultants for the purpose of conducting the Clinical Trial to maintain their compliance with the obligations stated herein, as required, or as needed to comply with

applicable laws.

14.2 With respect to any proposed presentation, publication, or abstract of the Data pursuant to this Section 15, the submitting party will submit to the other Party a copy of the proposed presentation, publication, or abstract and the name of the scientific journal or forum to which the proposed presentation, publication, or abstract will be submitted (b)(4) (b)(4) for abstracts prior to the submission thereof for presentation, publication, or abstract. (b)(4) (b)(4)

14.3 Each Party will provide, and RECIPIENT shall ensure that any Study Center, Investigator, or third party collaborator will provide, a copy of any proposed press release related to the Data to the other Party and to BARDA for review and comment at least five (5) calendar days in advance of the proposed press release. Each Party agrees that, following the receiving Party's review of the proposed press release for the maximum period of time specified above, if no comment is received by the submitting Party and/or the Study Centers or Investigators, the submitting Party, Investigators or Study Centers will be free to publish the press release.

15. GENERAL

15.1 No modification or amendment of this Agreement shall be effective unless made in writing and duly executed by an authorized signatory on behalf of each Party.

15.2 This Agreement constitutes the entire understanding among the Parties with respect to the subject matter hereof and supersedes all prior agreements and understandings between the Parties, whether written or oral, relating to the subject matter hereof.

15.3 Upon termination or expiration of this Agreement, Sections 7.2, 8.5, 9, 10, 11, 12, 13, 14, 15 and 16 shall continue in full force and effect.

15.4 This Agreement will be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

15.5 This Agreement shall not confer any rights or remedies upon any person or entity other than the Parties and their respective successors and permitted assigns.

15.6 This Agreement may be executed simultaneously in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

15.7 The section headings in this Agreement are inserted for convenience only.

15.8 Any term or provision of this Agreement that is invalid or unenforceable in any situation in any jurisdiction shall not affect the validity or enforceability of the remaining terms and provisions or the validation or enforceability of the offending term or provision in any other situation or in any other jurisdiction.

15.9 No failure on the part of either Party to exercise, and no delay in exercising, any right or remedy hereunder shall operate as a waiver thereof; nor shall any single or partial exercise of any right or remedy hereunder preclude any other or further exercise thereof or the exercise of any other right or remedy granted hereby or by any related document or by law.

15.10 Neither Party shall assign or transfer its interest in this Agreement or any portion thereof without the prior written consent of the other.

15.11 Each person signing this Agreement hereby certifies that he or she is duly authorized to execute this Agreement on behalf of the respective Party.

15.12 Neither Party shall be held liable to the other for failure of performance where such failure is caused solely by supervening conditions beyond the Party's reasonable control, including acts of God, civil disturbances, strikes, labor disputes, and lawful government action.

15.13 The Parties have participated jointly in the negotiation and drafting of this Agreement; therefore, no presumption or burden of proof shall arise favoring or disfavoring either Party based on authorship or drafting of any provision of this Agreement.

15.14 All notices or other communications required or permitted to be made or given hereunder shall be deemed so made or given when hand-delivered or sent in writing by registered or certified mail, postage prepaid and return-receipt requested, or by a recognized courier service, charges prepaid, and properly addressed to such other party as set forth below:

GILEAD:

(b)(6)
(b)(4)
333 Lakeside Drive,
Foster City, CA 94404

With copies to:

Gilead Sciences, Inc
333 Lakeside Drive
Foster City, California 94404
Attention: Clinical Legal
Facsimile: (b)(4)
Email: (b)(4)

and

RECIPIENT:

For NCATS :

(b)(6)
NCATS
National Institutes of Health
Department of Health and Human Services
6701 Democracy Blvd, Suite 900
Bethesda, MD 20817
Phone: (b)(6)
Email: (b)(6) @nih.gov

For Legal Notices:

(b)(6)
Director Office of Strategic Alliances
National Center for Advancing Translational Sciences, NIH
9800 Medical Center Drive, Room 340B
Rockville, MD 20850
Phone: (b)(6)
Email: (b)(6) @nih.gov

For regulatory matters:

(b)(6)
NCATS
National Institutes of Health
Department of Health and Human Services
6701 Democracy Blvd, Suite 900
Bethesda, MD 20817
Phone: (b)(6)

Email: (b)(6) @nih.gov

For clinical matters:

(b)(6)
NCATS
National Institutes of Health
Department of Health and Human Services
6701 Democracy Blvd. Suite 900
Bethesda, MD 20817
Phone: (b)(6)
Email (b)(6) @nih.gov

IN WITNESS WHEREOF, the undersigned have executed this Agreement as the date first written above.

GILEAD SCIENCES, INC.

By: (b)(6)

(b)(5)

(b)(6)

Date: 10 October 2020

THE NATIONAL CENTER ON ADVANCING TRANSLATIONAL SCIENCES

By: (b)(6)

Digitally signed by (b)(6)
Date: 2020.10.08 13:58:48 -04'00'

(b)(6) Executive Officer, NCATS for)
(b)(6)
Deputy Director
NCATS, National Institutes of Health, DHHS
6701 Democracy Blvd., Suite 900
Bethesda, MD 20817

Date: October 8, 2020

BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY

– Read and Acknowledged

(b)(6) Digitally signed by (b)(6)
Date: 2020.10.09 16:20:33 -04'00'

By: _____
(b)(6)

Director, Division or Clinical Development
Biomedical Advanced Research and Development Authority, DHHS

Date: _____

TECHNICAL RESOURCES INTERNATIONAL

– Read and Acknowledged

(b)(6) Digitally signed by (b)(6)
Date: 2020.10.08 14:25:27 -04'00'

By: _____
(b)(6) Director of Contracts
Technical Resources International, Inc.
6500 Rock Spring Drive, Suite 650
Bethesda, Maryland 20817

Date: _____